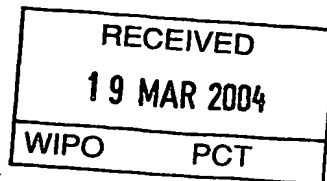
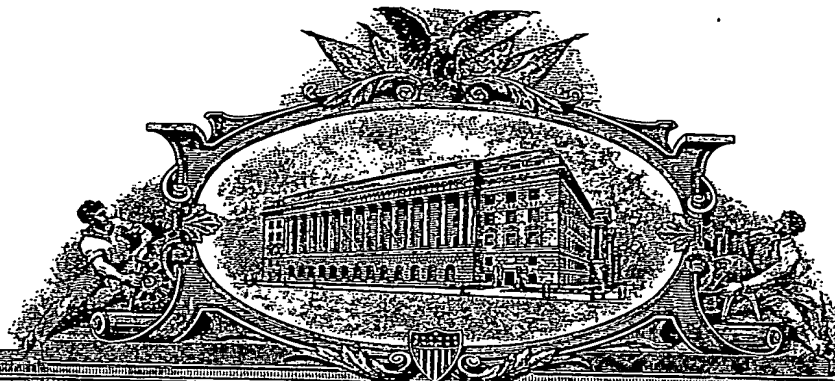


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# PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

INVENTOR(S)					
Given Name (first and middle (if any))		Family Name or Surname		Residence (City and either State or Foreign Country)	
Anthony G.M.		Barrett		London, England	
<input type="checkbox"/> Additional inventors are being named on the _____ separately numbered sheets attached hereto					
TITLE OF THE INVENTION (280 characters max) PROCESS FOR PREPARING TRANS-(1S,2S)-AMINOCYCLOHEXYL ETHER COMPOUNDS					
Direct all correspondence to: CORRESPONDENCE ADDRESS					
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Dowell & Dowell, P.C.					
Address		Suite 309, 1215 Jefferson Davis Hwy.			
Address					
City		Arlington	State	VA	ZIP
Country		U.S.A.	Telephone	(703) 415-2555	Fax
				(703) 415-2559	
ENCLOSED APPLICATION PARTS (check all that apply)					
<input checked="" type="checkbox"/>	Specification	Number of Pages	22	<input type="checkbox"/>	CD(s), Number
<input checked="" type="checkbox"/>	Drawing(s)	Number of Sheets	47	<input type="checkbox"/>	Other (specify)
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The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.					
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Respectfully submitted,

SIGNATURE

TYPED or PRINTED NAME

TELEPHONE

*Ralph A. Dowell*

Ralph A. Dowell

703 415 2555

Date

05 June 03

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P19SMALL/REV05

# PROCESS FOR PREPARING TRANS-(1S,2S)-AMINOCYCLOHEXYL ETHER COMPOUNDS

## FIELD OF THE INVENTION

The present invention is generally directed toward a process for the preparation of stereoisomerically substantially pure trans-(1S,2S)-aminocyclohexyl ether compounds as well as various intermediates and substrates involved.

## BRIEF DESCRIPTION OF THE DRAWINGS

Scheme 1 illustrates a general reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1S,2S)-aminocyclohexyl ether compound of formula (10).

Scheme 2A illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1S,2S)-aminocyclohexylether compound of formula (20).

Scheme 2B illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1S,2S)-aminocyclohexylether compound of formula (20).

Scheme 3A illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1S,2S)-aminocyclohexylether compound of formula (24).

Scheme 3B illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1S,2S)-aminocyclohexylether compound of formula (24).

Scheme 4 illustrates a general reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1S,2S)-aminocyclohexyl ether compound of formula (10).

Scheme 5A illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1S,2S)-aminocyclohexylether compound of formula (20).

Scheme 5B illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1S,2S)-aminocyclohexylether compound of formula (20).

Scheme 6A illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1S,2S)-aminocyclohexylether compound of formula (24).

Scheme 6B illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1S,2S)-aminocyclohexylether compound of formula (24).

Scheme 7 illustrates a general reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1S,2S)-aminocyclohexyl ether compound of formula (10).

Scheme 8A illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1S,2S)-aminocyclohexylether compound of formula (20).

Scheme 8B illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1*S*,2*S*)-aminocyclohexylether compound of formula (20).

Scheme 9A illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1*S*,2*S*)-aminocyclohexylether compound of formula (24).

Scheme 9B illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1*S*,2*S*)-aminocyclohexylether compound of formula (24).

Scheme 10 illustrates a general reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1*S*,2*S*)-aminocyclohexyl ether compound of formula (10).

Scheme 11A illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1*S*,2*S*)-aminocyclohexylether compound of formula (20).

Scheme 11B illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1*S*,2*S*)-aminocyclohexylether compound of formula (20).

Scheme 12A illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1*S*,2*S*)-aminocyclohexylether compound of formula (24).

Scheme 12B illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1*S*,2*S*)-aminocyclohexylether compound of formula (24).

Scheme 13 illustrates a general reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1*S*,2*S*)-aminocyclohexyl ether compound of formula (10).

Scheme 14A illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1*S*,2*S*)-aminocyclohexylether compound of formula (20).

Scheme 14B illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1*S*,2*S*)-aminocyclohexylether compound of formula (20).

Scheme 15A illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1*S*,2*S*)-aminocyclohexylether compound of formula (24).

Scheme 15B illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1*S*,2*S*)-aminocyclohexylether compound of formula (24).

Scheme 16 illustrates a general reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1*S*,2*S*)-aminocyclohexyl ether compound of formula (10).

Scheme 17A illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1*S*,2*S*)-aminocyclohexylether compound of formula (20).

Scheme 17B illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1*S*,2*S*)-aminocyclohexylether compound of formula (20).

Scheme 18A illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1*S*,2*S*)-aminocyclohexylether compound of formula (24).

Scheme 18B illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1*S*,2*S*)-aminocyclohexylether compound of formula (24).

Scheme 19 illustrates a general reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1*S*,2*S*)-aminocyclohexyl ether compound of formula (10).

Scheme 20A illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1*S*,2*S*)-aminocyclohexylether compound of formula (20).

Scheme 20B illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1*S*,2*S*)-aminocyclohexylether compound of formula (20).

Scheme 21A illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1*S*,2*S*)-aminocyclohexylether compound of formula (24).

Scheme 21B illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1*S*,2*S*)-aminocyclohexylether compound of formula (24).

Scheme 22B illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1*S*,2*S*)-aminocyclohexylether compound of formula (20).

Scheme 23B illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1*S*,2*S*)-aminocyclohexylether compound of formula (24).

Scheme 24 illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure compound of formula (8).

Scheme 25A illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure compound of formula (18).

Scheme 25B illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure compound of formula (22).

Scheme 26B illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure compound of formula (26).

Scheme 27 illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure compound of formula (6).

Scheme 28A illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure compound of formula (16).

Scheme 29 illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure compound of formula (5).

Scheme 30A illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure compound of formula (15).

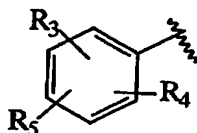
Scheme 31 illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure compound of formula (4).

Scheme 32A illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure compound of formula (14).

## DESCRIPTION OF THE INVENTION

### Definitions and Conventions

In the formulae depicted herein, a bond to a substituent and/or a bond that links a molecular fragment to the remainder of a compound may be shown as intersecting one or more bonds in a ring structure. This indicates that the bond may be attached to any one of the atoms that constitutes the ring structure, so long as a hydrogen atom could otherwise be present at that atom. Where no particular substituent(s) is identified for a particular position in a structure, then hydrogen(s) is present at that position. For example, compounds of the invention containing the following group:



are intended to encompass groups wherein any ring atom that could otherwise be substituted with hydrogen, may instead be substituted with either R<sub>3</sub>, R<sub>4</sub> or R<sub>5</sub>, with the proviso that each of R<sub>3</sub>, R<sub>4</sub> and R<sub>5</sub> appears once and only once on the ring. Ring atoms that are not substituted with any of R<sub>3</sub>, R<sub>4</sub> or R<sub>5</sub> are substituted with hydrogen. In those instances where the invention specifies that a non-aromatic ring is substituted with more than one R group, and those R groups are shown connected to the non-aromatic ring with bonds that bisect ring bonds, then the R groups may be present at different atoms of the ring, or on the same atom of the ring, so long as that atom could otherwise be substituted with a hydrogen atom.

When the invention specifies the location of an asymmetric divalent radical, then that divalent radical may be positioned in any possible manner that provides a stable chemical structure.

A wavy bond from a substituent to the central cyclohexane ring indicates that that group may be located on either side of the plane of the central ring.

The compounds of the present invention contain at least two asymmetric carbon atoms and thus can exist as enantiomers and diastereomers. Unless otherwise noted, the phrase "stereoisomerically substantially pure" generally refers to those asymmetric carbon atoms that are described or illustrated in the structural formulae for that compound.

The phrase "independently at each occurrence" is intended to mean (i) when any variable occurs more than one time in a compound of the invention, the definition of that variable at each occurrence is independent of its definition at every other occurrence; and (ii) the identity of any one of two different variables (*e.g.*,  $R_1$  within the set  $R_1$  and  $R_2$ ) is selected without regard of the identity of the other member of the set. However, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

In accordance with the present invention and as used herein, the following terms are defined to have following meanings, unless explicitly stated otherwise:

"Acid addition salts" refers to those salts which retain the biological effectiveness and properties of the free bases and which are not biologically or otherwise undesirable, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, or organic acids such as acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, *p*-toluenesulfonic acid, salicylic acid and the like.

"Acyl" refers to branched or unbranched hydrocarbon fragments terminated by a carbonyl  $-(C=O)-$  group containing the specified number of carbon atoms. Examples include acetyl [ $CH_3C(=O)-$ , a  $C_2$ acyl] and propionyl [ $CH_3CH_2C(=O)-$ , a  $C_3$ acyl].

"Alkanoyloxy" refers to an ester substituent wherein the non-carbonyl oxygen is the point of attachment to the molecule. Examples include propanoyloxy [ $(CH_3CH_2C(=O)-O-$ , a  $C_3$ alkanoyloxy] and ethanoyloxy [ $CH_3C(=O)-O-$ , a  $C_2$ alkanoyloxy].

"Alkoxy" refers to an O-atom substituted by an alkyl group, for example, methoxy [ $-OCH_3$ , a  $C_1$ alkoxy].

"Alkoxyalkyl" refers to an alkylene group substituted with an alkoxy group. For example, methoxyethyl [ $CH_3OCH_2CH_2-$ ] and ethoxymethyl ( $CH_3CH_2OCH_2-$ ) are both  $C_3$ alkoxyalkyl groups.

"Alkoxycarbonyl" refers to an ester substituent wherein the carbonyl carbon is the point of attachment to the molecule. Examples include ethoxycarbonyl [ $CH_3CH_2OC(=O)-$ , a  $C_3$ alkoxycarbonyl] and methoxycarbonyl [ $CH_3OC(=O)-$ , a  $C_2$ alkoxycarbonyl].

"Alkyl" refers to a branched or unbranched hydrocarbon fragment containing the specified number of carbon atoms and having one point of attachment. Examples include *n*-propyl (a C<sub>3</sub>alkyl), *iso*-propyl (also a C<sub>3</sub>alkyl), and *t*-butyl (a C<sub>4</sub>alkyl). Methyl is represented by the symbol Me or CH<sub>3</sub>.

"Alkylene" refers to a divalent radical which is a branched or unbranched hydrocarbon fragment containing the specified number of carbon atoms, and having two points of attachment. An example is propylene [-CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-, a C<sub>3</sub>alkylene].

"Alkylcarboxy" refers to a branched or unbranched hydrocarbon fragment terminated by a carboxylic acid group [-COOH]. Examples include carboxymethyl [HOOC-CH<sub>2</sub>-, a C<sub>2</sub>alkylcarboxy] and carboxyethyl [HOOC-CH<sub>2</sub>CH<sub>2</sub>-, a C<sub>3</sub>alkylcarboxy].

"Aryl" refers to aromatic groups which have at least one ring having a conjugated pi electron system and includes carbocyclic aryl, heterocyclic aryl (also known as heteroaryl groups) and biaryl groups, all of which may be optionally substituted. Carbocyclic aryl groups are generally preferred in the compounds of the present invention, where phenyl and naphthyl groups are preferred carbocyclic aryl groups.

"Aralkyl" refers to an alkylene group wherein one of the points of attachment is to an aryl group. An example of an aralkyl group is the benzyl group (Bn) [C<sub>6</sub>H<sub>5</sub>CH<sub>2</sub>-, a C<sub>7</sub>aralkyl group].

"Cycloalkyl" refers to a ring, which may be saturated or unsaturated and monocyclic, bicyclic, or tricyclic formed entirely from carbon atoms. An example of a cycloalkyl group is the cyclopentenyl group (C<sub>5</sub>H<sub>7</sub>-), which is a five carbon (C<sub>5</sub>) unsaturated cycloalkyl group.

"Carbocyclic" refers to a ring which may be either an aryl ring or a cycloalkyl ring, both as defined above.

"Carbocyclic aryl" refers to aromatic groups wherein the atoms which form the aromatic ring are carbon atoms. Carbocyclic aryl groups include monocyclic carbocyclic aryl groups such as phenyl, and bicyclic carbocyclic aryl groups such as naphthyl, all of which may be optionally substituted.

"Heteroatom" refers to a non-carbon atom, where boron, nitrogen, oxygen, sulfur and phosphorus are preferred heteroatoms, with nitrogen, oxygen and sulfur being particularly preferred heteroatoms in the compounds of the present invention.

"Heteroaryl" refers to aryl groups having from 1 to 9 carbon atoms and the remainder of the atoms are heteroatoms, and includes those heterocyclic systems described in "Handbook of Chemistry and Physics," 49th edition, 1968, R.C. Weast, editor; The Chemical Rubber Co., Cleveland, OH. See particularly Section C, Rules for Naming Organic Compounds, B. Fundamental Heterocyclic Systems.



Suitable heteroaryls include furanyl, thienyl, pyridyl, pyrrolyl, pyrimidyl, pyrazinyl, imidazolyl, and the like.

"Hydroxyalkyl" refers to a branched or unbranched hydrocarbon fragment bearing an hydroxy (-OH) group. Examples include hydroxymethyl (-CH<sub>2</sub>OH, a C<sub>1</sub>hydroxyalkyl) and 1-hydroxyethyl (-CHOHCH<sub>3</sub>, a C<sub>2</sub>hydroxyalkyl).

"Thioalkyl" refers to a sulfur atom substituted by an alkyl group, for example thiomethyl (CH<sub>3</sub>S-, a C<sub>1</sub>thioalkyl).

"Modulating" in connection with the activity of an ion channel means that the activity of the ion channel may be either increased or decreased in response to administration of a compound or composition or method of the present invention. Thus, the ion channel may be activated, so as to transport more ions, or may be blocked, so that fewer or no ions are transported by the channel.

"Pharmaceutically acceptable carriers" for therapeutic use are well known in the pharmaceutical art, and are described, for example, in Remingtons Pharmaceutical Sciences, Mack Publishing Co. (A.R. Gennaro edit. 1985). For example, sterile saline and phosphate-buffered saline at physiological pH may be used. Preservatives, stabilizers, dyes and even flavoring agents may be provided in the pharmaceutical composition. For example, sodium benzoate, sorbic acid and esters of *p*-hydroxybenzoic acid may be added as preservatives. *Id.* at 1449. In addition, antioxidants and suspending agents may be used. *Id.*

"Pharmaceutically acceptable salt" refers to salts of the compounds of the present invention derived from the combination of such compounds and an organic or inorganic acid (acid addition salts) or an organic or inorganic base (base addition salts). The compounds of the present invention may be used in either the free base or salt forms, with both forms being considered as being within the scope of the present invention.

The "therapeutically effective amount" of a compound of the present invention will depend on the route of administration, the type of warm-blooded animal being treated, and the physical characteristics of the specific warm-blooded animal under consideration. These factors and their relationship to determining this amount are well known to skilled practitioners in the medical arts. This amount and the method of administration can be tailored to achieve optimal efficacy but will depend on such factors as weight, diet, concurrent medication and other factors which those skilled in the medical arts will recognize.

Compositions described herein as "containing a compound of the present invention" encompass compositions that may contain more than one compound of the present invention formula.

The synthetic procedures described herein, especially when taken with the general knowledge in the art, provide sufficient guidance to perform the synthesis, isolation, and purification of the compounds of the present invention.

The following examples are offered by way of illustration and not by way of limitation. Unless otherwise specified, starting materials and reagents may be obtained from well-known commercial supply houses, *e.g.*, Aldrich Chemical Company (Milwaukee, WI), and are of standard grade and purity; or may be obtained by procedures described in the art or adapted therefrom, where suitable procedures may be identified through the Chemical Abstracts and Indices therefor, as developed and published by the American Chemical Society.

#### Outline of Some General Reaction Processes of the Invention

The aminocyclohexyl ether compounds of the present invention contain ether and amino functional groups disposed in a 1,2 arrangement on a cyclohexane ring. Accordingly, the ether and amino functional groups may be disposed in either a *cis* or *trans* relationship, relative to one another and the plane of the cyclohexane ring. The present invention provides synthetic processes whereby compounds of formula (10) with *trans*-(1*S*,2*S*) configuration for the ether and amino functional groups may be prepared in stereoisomerically substantially pure form. Compounds of formulae (20), (22), (24) and (26) are some of the examples represented by formula (10). The present invention also provides synthetic processes whereby compounds of formulae (4), (5), (6) and (8) may be synthesized in stereoisomerically substantially pure forms. Compounds (14), (15), (16) and (18) are examples of formulae (4), (5), (6) and (8) respectively.

As outlined in Scheme 1, the preparation of a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (10) may be carried out by following a process starting with a monohalobenzene (1), wherein X may be F, Cl, Br or I.

In a first step, compound (1) is transformed by well-established microbial oxidation to the *cis*-cyclohexandienediol (2) in stereoisomerically substantially pure form (T. Hudlicky et al., *Aldrichimica Acta*, 1999, 32, 35; and references cited therein). In a separate step, the less hindered hydroxy function in compound (2) may be selectively monoprotected as compound (3) where Pro represents the appropriate protecting group of the hydroxy function with retention of stereochemistry (T. Hudlicky et al., *Aldrichimica Acta*, 1999, 32, 35; S.M. Brown and T. Hudlicky, In *Organic Synthesis: Theory and Applications*; T. Hudlicky, Ed.; JAI Press: Greenwich, CT, 1993; Vol. 2, p 113; and references cited therein). Tri-alkyl-silyl groups such as tri-isopropyl-silyl (TIPS) and t-butyl dimethylsilyl

(TBDMS) and alkyl-diaryl-silyl groups such as t-butyldiphenylsilyl (TBDPS) are some of the possible examples for Pro. Suitable reaction conditions are set forth in, for example, Greene, "Protective Groups in Organic Chemistry", John Wiley & Sons, New York NY (1991). In a separate step, conversion of compound (3) to compound (4) may be effected by hydrogenation and hydrogenolysis in the presence of a catalyst under appropriate conditions. Palladium on activated carbon is one example of the catalysts. Hydrogenolysis of alkyl or alkenyl halide such as (3) may be conducted under basic conditions. The presence of a base such as sodium ethoxide, sodium bicarbonate, sodium acetate or calcium carbonate is some possible examples. The base may be added in one portion or incrementally during the course of the reaction. In a separate step, the free hydroxy group of compound (4) is converted into an activated form as represented by formula (5) under suitable conditions. An "activated form" as used herein means that the hydroxy group is converted into a good leaving group ( $-O-J$ ). The leaving group may be a mesylate ( $MsO-$ ) group, a tosylate group ( $TsO-$ ) or a nosylate ( $NsO-$ ). The hydroxy group may also be converted into other suitable leaving groups according to procedures well known in the art. In a typical reaction for the formation of a tosylate, compound (4) is treated with a hydroxy activating reagent such as tosyl chloride ( $TsCl$ ) in the presence of a base, such as pyridine or triethylamine. The reaction is generally satisfactorily conducted at about  $0^{\circ}C$ , but may be adjusted as required to maximize the yields of the desired product. An excess of the hydroxy activating reagent (e.g. tosyl chloride), relative to compound (4) may be used to maximally convert the hydroxy group into the activated form. In a separate step, removal of the protecting group (Pro) in compound (5) by standard procedures (e.g. tetrabutylammonium fluoride in tetrahydrofuran or as described in Greene, "Protective Groups in Organic Chemistry", John Wiley & Sons, New York NY (1991)) affords compound (6). In a separate step, alkylation of the free hydroxy group in compound (6) to form compound (8) is carried out under appropriate conditions with compound (7), where  $-O-Q$  represents a good leaving group on reaction with a hydroxy function with retention of the stereochemical configuration of the hydroxy function in the formation of an ether compound. Trichloroacetimidate is one example for the  $-O-Q$  function. For some compound (7), it may be necessary to introduce appropriate protection groups prior to this step being performed. Suitable protecting groups are set forth in, for example, Greene, "Protective Groups in Organic Chemistry", John Wiley & Sons, New York NY (1991).

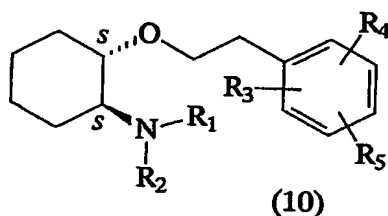
In a separate step, the resulted compound (8) is treated under suitable conditions with an amino compound of formula (9) to form compound (10) as the product. The reaction may be carried out with or without a solvent and at an appropriate temperature range that allows the formation of the product (10) at a suitable rate. An excess of the amino compound (9) may be used to maximally convert

compound (8) to the product (10). The reaction may be performed in the presence of a base that can facilitate the formation of the product. Generally the base is non-nucleophilic in chemical reactivity. When the reaction has proceeded to substantial completion, the product is recovered from the reaction mixture by conventional organic chemistry techniques, and is purified accordingly. Protective groups may be removed at the appropriate stage of the reaction sequence. Suitable methods are set forth in, for example, Greene, "Protective Groups in Organic Chemistry", John Wiley & Sons, New York NY (1991).

The reaction sequence described above (Scheme 1) generates the compound of formula (10) as the free base. The free base may be converted, if desired, to the monohydrochloride salt by known methodologies, or alternatively, to other acid addition salts by reaction with an inorganic or organic acid under appropriate conditions. Acid addition salts can also be prepared metathetically by reaction of one acid addition salt with an acid that is stronger than that giving rise to the initial salt.

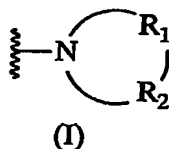
All publications and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication or patent application is specifically and individually incorporated by reference.

In one aspect, the present invention provides a process for the preparation of a stereoisomerically substantially pure compound of formula (10):



wherein, independently at each occurrence,  $R_1$  and  $R_2$  are independently selected from hydrogen,  $C_1$ - $C_8$ alkyl,  $C_3$ - $C_8$ alkoxyalkyl,  $C_1$ - $C_8$ hydroxyalkyl, and  $C_7$ - $C_{12}$ aralkyl; or

$R_1$  and  $R_2$ , when taken together with the nitrogen atom to which they are directly attached in formula (10), form a ring denoted by formula (I):



wherein the ring of formula (I) is formed from the nitrogen as shown as well as three to nine additional ring atoms independently selected from carbon, nitrogen, oxygen, and sulfur; where any two adjacent ring atoms may be joined together by single or double bonds, and where any one or more of the additional

carbon ring atoms may be substituted with one or two substituents selected from hydrogen, hydroxy, C<sub>1</sub>-C<sub>3</sub>hydroxyalkyl, oxo, C<sub>2</sub>-C<sub>4</sub>acyl, C<sub>1</sub>-C<sub>3</sub>alkyl, C<sub>2</sub>-C<sub>4</sub>alkylcarboxy, C<sub>1</sub>-C<sub>3</sub>alkoxy, C<sub>1</sub>-C<sub>20</sub>alkanoyloxy, or may be substituted to form a spiro five- or six-membered heterocyclic ring containing one or two heteroatoms selected from oxygen and sulfur; and any two adjacent additional carbon ring atoms may be fused to a C<sub>3</sub>-C<sub>8</sub>carbocyclic ring, and any one or more of the additional nitrogen ring atoms may be substituted with substituents selected from hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>2</sub>-C<sub>4</sub>acyl, C<sub>2</sub>-C<sub>4</sub>hydroxyalkyl and C<sub>3</sub>-C<sub>8</sub>alkoxyalkyl; or

R<sub>1</sub> and R<sub>2</sub>, when taken together with the nitrogen atom to which they are directly attached in formula (I), may form a bicyclic ring system selected from 3-azabicyclo[3.2.2]nonan-3-yl, 2-azabicyclo[2.2.2]octan-2-yl, 3-azabicyclo[3.1.0]hexan-3-yl, and 3-azabicyclo[3.2.0]heptan-3-yl;

R<sub>3</sub>, R<sub>4</sub> and R<sub>5</sub> are independently selected from bromine, chlorine, fluorine, carboxy, hydrogen, hydroxy, hydroxymethyl, methanesulfonamido, nitro, cyano, sulfamyl, trifluoromethyl, C<sub>2</sub>-C<sub>7</sub>alkanoyloxy, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>alkoxy, C<sub>2</sub>-C<sub>7</sub>alkoxycarbonyl, C<sub>1</sub>-C<sub>6</sub>thioalkyl, aryl and N(R<sub>6</sub>,R<sub>7</sub>) where R<sub>6</sub> and R<sub>7</sub> are independently selected from hydrogen, acetyl, methanesulfonyl, and C<sub>1</sub>-C<sub>6</sub>alkyl;

comprising the steps of starting with a monohalobenzene (1), wherein X may be F, Cl, Br or I; and following a reaction sequence as outlined in Scheme 1 under suitable conditions, wherein

Pro represents the appropriate protecting group of the hydroxy function with retention of stereochemistry;

-O-Q represents a good leaving group on reaction with a hydroxy function under suitable conditions with retention of the stereochemical configuration of the hydroxy function in the formation of an ether compound; and

-O-J represents a good leaving group on reaction with a nucleophilic reactant under suitable conditions with inversion of the stereochemical configuration as illustrated in Scheme 1 and all the formulae and symbols are as described above.

In another aspect, the present invention provides a process for the preparation of a stereoisomerically substantially pure compound of formula (20), comprising the steps under suitable conditions as shown in Scheme 2A, wherein all the formulae and symbols are as described above. As outlined in Scheme 2A, the preparation of a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (20) may be carried out by starting with a biotransformation of chlorobenzene (1) to compound (12) by microorganism such as *Pseudomonas putida* 39/D. Experimental conditions for the biotransformation are well established (Organic Synthesis, Vol. 76, 77 and T. Hudlicky et al., Aldrichimica Acta, 1999, 32, 35; and references cited therein). In a separate step, the less hindered

hydroxy function in compound (12) is selectively monosilylated as compound (13) by reaction with silylating reagent such as t-butyldiphenylsilyl chloride (TBDPSCI) under suitable conditions (e.g. imidazole in  $\text{CH}_2\text{Cl}_2$ ) (T. Hudlicky et al., *Aldrichimica Acta*, 1999, 32, 35; S.M. Brown and T. Hudlicky, *In Organic Synthesis: Theory and Applications*; T. Hudlicky, Ed.; JAI Press: Greenwich, CT, 1993; Vol. 2, p 113; and references cited therein). In another separate step, compound (13) is converted to compound (14) by reduction such as hydrogenation and hydrogenolysis in the presence of a catalyst under appropriate conditions. Palladium on activated carbon is one example of the catalysts. The reduction of compound (13) may be conducted under basic conditions e.g. in the presence of a base such as sodium ethoxide, sodium bicarbonate, sodium acetate or calcium carbonate. The base may be added in one portion or incrementally during the course of the reaction. In a separate step, the hydroxy group of compound (14) is converted under suitable conditions into an activated form such as the tosylate of formula (15) by treatment with tosyl chloride (TsCl) in the presence of pyridine. In another separate step, the t-butyldiphenylsilyl (TBDPS) protection group in compound (15) may be removed by standard procedures (e.g. tetrabutylammonium fluoride in tetrahydrofuran or as described in Greene, "Protective Groups in Organic Chemistry", John Wiley & Sons, New York NY (1991)) to afford the hydroxytosylate compound (16). In a separate step, the free hydroxy group in compound (16) is alkylated under appropriate conditions to form compound (18). The trichloroacetimidate (17) is readily prepared from the corresponding alcohol, 3,4-dimethoxyphenethyl alcohol which is commercially available (e.g. Aldrich), by treatment with trichloroacetonitrile. The alkylation of compound (16) by trichloroacetimidate (17) may be carried out in the presence of a Lewis acid such as  $\text{HBF}_4$ . In another separate step, the tosylate group of formula (18) is displaced by an amino compound such as 3*R*-pyrrolidinol (19) with inversion of configuration. 3*R*-pyrrolidinol (19) is commercially available (e.g. Aldrich) or may be prepared according to published procedure (e.g. *Chem.Ber./Recueil* 1997, 130, 385-397). The reaction may be carried out with or without a solvent and at an appropriate temperature range that allows the formation of the product (20) at a suitable rate. An excess of the amino compound (19) may be used to maximally convert compound (18) to the product (20). The reaction may be performed in the presence of a base that can facilitate the formation and isolation of the product. Generally the additional base is non-nucleophilic in chemical reactivity. When the reaction has proceeded to substantial completion, the desired product is recovered from the reaction mixture by conventional organic chemistry techniques, and is purified accordingly.

The reaction sequence described above (Scheme 2A) in general generates the compound of formula (20) as the free base. The free base may be converted, if desired, to the monohydrochloride salt

by known methodologies, or alternatively, to other acid addition salts by reaction with an inorganic or organic acid under appropriate conditions. Acid addition salts can also be prepared metathetically by reaction of one acid addition salt with an acid that is stronger than that giving rise to the initial salt.

In another aspect, the preparation of a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (20) may be carried out by a process as outlined in Scheme 2B, comprising the steps of starting with chlorobenzene (11) and following a reaction sequence under suitable conditions analogous to the applicable portion that is described in Scheme 2A above leading to compound of formula (18). The latter is reacted with an amino compound of formula (21) wherein Bn represents a benzyl protection group of the hydroxy function of 3*R*-pyrrolidinol to form compound (22). Compound (21) is commercially available (e.g. Aldrich) or may be prepared according to published procedure (e.g. Chem.Ber./Recueil 1997, 130, 385-397). The reaction may be carried out with or without a solvent and at an appropriate temperature range that allows the formation of the product (21) at a suitable rate. An excess of the amino compound (21) may be used to maximally convert compound (18) to the product (22). The reaction may be performed in the presence of a base that can facilitate the formation of the product. Generally the additional base is non-nucleophilic in chemical reactivity. The benzyl (Bn) protection group of compound (22) may be removed by standard procedure (e.g. hydrogenation in the presence of a catalyst under appropriate conditions. Palladium on activated carbon is one example of the catalysts. Other suitable conditions are as described in Greene, "Protective Groups in Organic Chemistry", John Wiley & Sons, New York NY (1991)). The product is a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (20) and is generally formed as the free base. The free base may be converted, if desired, to the monohydrochloride salt by known methodologies, or alternatively, to other acid addition salts by reaction with an inorganic or organic acid under appropriate conditions. Acid addition salts can also be prepared metathetically by reaction of one acid addition salt with an acid that is stronger than that giving rise to the initial salt.

In another aspect, the preparation of a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (24) may be carried out by a process as outlined in Scheme 3A, comprising the steps of starting with chlorobenzene (11) and following a reaction sequence under suitable conditions analogous to the applicable portion that is described in Scheme 2A above leading to compound of formula (18). The latter is reacted with an amino compound of formula (23). Compound (23), 3*S*-pyrrolidinol, is commercially available (e.g. Aldrich) or may be prepared according to published procedure (e.g. Chem.Ber./Recueil 1997, 130, 385-397). The reaction may be carried out with or without a solvent and at an appropriate temperature range that allows the formation of the product (24) at a suitable rate. An

excess of the amino compound (23) may be used to maximally convert compound (18) to the product (24). The reaction may be performed in the presence of a base that can facilitate the formation of the product. Generally the additional base is non-nucleophilic in chemical reactivity. The product is a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (24) and is formed as the free base. The free base may be converted, if desired, to the monohydrochloride salt by known methodologies, or alternatively, to other acid addition salts by reaction with an inorganic or organic acids under appropriate conditions. Acid addition salts can also be prepared metathetically by reaction of one acid addition salt with an acid that is stronger than that giving rise to the initial salt.

In another aspect, the preparation of a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (24) may be carried out by a process as outlined in Scheme 3B, comprising the steps of starting with chlorobenzene (11) and following a reaction sequence under suitable conditions analogous to the applicable portion that is described in Scheme 2B above leading to compound of formula (18). The latter is reacted with an amino compound of formula (25) wherein Bn represents a benzyl protection group of the hydroxy function of 3S-pyrrolidinol to form compound (26). Compound (25) is commercially available (e.g. Aldrich) or may be prepared according to published procedure (e.g. Chem.Ber./Recueil 1997, 130, 385-397). The reaction may be carried out with or without a solvent and at an appropriate temperature range that allows the formation of the product (26) at a suitable rate. An excess of the amino compound (25) may be used to maximally convert compound (18) to the product (26). The reaction may be performed in the presence of a base that can facilitate the formation of the product. Generally the additional base is non-nucleophilic in chemical reactivity. The benzyl (Bn) protection group of compound (26) may be removed by standard procedure (e.g. hydrogenation in the presence of a catalyst under appropriate conditions. Palladium on activated carbon is one example of the catalysts. Other suitable conditions are as described in Greene, "Protective Groups in Organic Chemistry", John Wiley & Sons, New York NY (1991)). The product is a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (24) and is formed as the free base. The free base may be converted, if desired, to the monohydrochloride salt by known methodologies, or alternatively, to other acid addition salts by reaction with an inorganic or organic acids under appropriate conditions. Acid addition salts can also be prepared metathetically by reaction of one acid addition salt with an acid that is stronger than that giving rise to the initial salt.

In another aspect, the preparation of a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (10) may be carried out by a process as outlined in Scheme 4, comprising the steps of starting with compound of formula (2) and following a reaction sequence under suitable



conditions analogous to the applicable portion that is described in Scheme 1, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (20) may be carried out by a process as outlined in Scheme 5A, comprising the steps of starting with compound of formula (12) and following a reaction sequence under suitable conditions analogous to the applicable portion that is described in Scheme 2A, wherein all the formulae and symbols are as described above. 3-Chloro-(1*S*,2*S*)-3,5-cyclohexadiene-1,2-diol of formula (12) is a commercially available product (e.g. Aldrich) or synthesized according to published procedure (e.g. Organic Synthesis, Vol. 76, 77 and T. Hudlicky et al., *Aldrichimica Acta*, 1999, 32, 35; and references cited therein).

In another aspect, the preparation of a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (20) may be carried out by a process as outlined in Scheme 5B, comprising the steps of starting with compound of formula (12) and following a reaction sequence under suitable conditions analogous to the applicable portion that is described in Scheme 2B, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (24) may be carried out by a process as outlined in Scheme 6A, comprising the steps of starting with compound of formula (12) and following a reaction sequence under suitable conditions analogous to the applicable portion that is described in Scheme 3A, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (24) may be carried out by a process as outlined in Scheme 6B, comprising the steps of starting with compound of formula (12) and following a reaction sequence under suitable conditions analogous to the applicable portion that is described in Scheme 3B, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (10) may be carried out by a process as outlined in Scheme 7, comprising the steps of starting with compound of formula (3) and following a reaction sequence under suitable conditions analogous to the applicable portion that is described in Scheme 1, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (20) may be carried out by a process as outlined in Scheme 8A, comprising

the steps of starting with compound of formula (13) and following a reaction sequence under suitable conditions analogous to the applicable portion that is described in Scheme 2A, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (20) may be carried out by a process as outlined in Scheme 8B, comprising the steps of starting with compound of formula (13) and following a reaction sequence under suitable conditions analogous to the applicable portion that is described in Scheme 2B, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (24) may be carried out by a process as outlined in Scheme 9A, comprising the steps of starting with compound of formula (13) and following a reaction sequence under suitable conditions analogous to the applicable portion that is described in Scheme 3A, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (24) may be carried out by a process as outlined in Scheme 9B, comprising the steps of starting with compound of formula (13) and following a reaction sequence under suitable conditions analogous to the applicable portion that is described in Scheme 3B, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (10) may be carried out by a process as outlined in Scheme 10, comprising the steps of starting with compound of formula (4) and following a reaction sequence under suitable conditions analogous to the applicable portion that is described in Scheme 1, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (20) may be carried out by a process as outlined in Scheme 11A, comprising the steps of starting with compound of formula (14) and following a reaction sequence under suitable conditions analogous to the applicable portion that is described in Scheme 2A, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (20) may be carried out by a process as outlined in Scheme 11B, comprising the steps of starting with compound of formula (14) and following a reaction sequence under suitable

conditions analogous to the applicable portion that is described in Scheme 2B, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (24) may be carried out by a process as outlined in Scheme 12A, comprising the steps of starting with compound of formula (14) and following a reaction sequence under suitable conditions analogous to the applicable portion that is described in Scheme 3A, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (24) may be carried out by a process as outlined in Scheme 12B, comprising the steps of starting with compound of formula (14) and following a reaction sequence under suitable conditions analogous to the applicable portion that is described in Scheme 3B, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (10) may be carried out by a process as outlined in Scheme 13, comprising the steps of starting with compound of formula (5) and following a reaction sequence under suitable conditions analogous to the applicable portion that is described in Scheme 1, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (20) may be carried out by a process as outlined in Scheme 14A, comprising the steps of starting with compound of formula (15) and following a reaction sequence under suitable conditions analogous to the applicable portion that is described in Scheme 2A, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (20) may be carried out by a process as outlined in Scheme 14B, comprising the steps of starting with compound of formula (15) and following a reaction sequence under suitable conditions analogous to the applicable portion that is described in Scheme 2B, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (24) may be carried out by a process as outlined in Scheme 15A, comprising the steps of starting with compound of formula (15) and following a reaction sequence under suitable conditions analogous to the applicable portion that is described in Scheme 3A, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (24) may be carried out by a process as outlined in Scheme 15B, comprising the steps of starting with compound of formula (15) and following a reaction sequence under suitable conditions analogous to the applicable portion that is described in Scheme 3B, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (10) may be carried out by a process as outlined in Scheme 16, comprising the steps of starting with compound of formula (6) and following a reaction sequence under suitable conditions analogous to the applicable portion that is described in Scheme 1, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (20) may be carried out by a process as outlined in Scheme 17A, comprising the steps of starting with compound of formula (16) and following a reaction sequence under suitable conditions analogous to the applicable portion that is described in Scheme 2A, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (20) may be carried out by a process as outlined in Scheme 17B, comprising the steps of starting with compound of formula (16) and following a reaction sequence under suitable conditions analogous to the applicable portion that is described in Scheme 2B, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (24) may be carried out by a process as outlined in Scheme 18A, comprising the steps of starting with compound of formula (16) and following a reaction sequence under suitable conditions analogous to the applicable portion that is described in Scheme 3A, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (24) may be carried out by a process as outlined in Scheme 18B, comprising the steps of starting with compound of formula (16) and following a reaction sequence under suitable conditions analogous to the applicable portion that is described in Scheme 3B, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (10) may be carried out by a process as outlined in Scheme 19, comprising the

steps of starting with compound of formula (8) and following a reaction sequence under suitable conditions analogous to the applicable portion that is described in Scheme 1, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (20) may be carried out by a process as outlined in Scheme 20A, comprising the steps of starting with compound of formula (18) and following a reaction sequence under suitable conditions analogous to the applicable portion that is described in Scheme 2A, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (20) may be carried out by a process as outlined in Scheme 20B, comprising the steps of starting with compound of formula (18) and following a reaction sequence under suitable conditions analogous to the applicable portion that is described in Scheme 2B, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (24) may be carried out by a process as outlined in Scheme 21A, comprising the steps of starting with compound of formula (18) and following a reaction sequence under suitable conditions analogous to the applicable portion that is described in Scheme 3A, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (24) may be carried out by a process as outlined in Scheme 21B, comprising the steps of starting with compound of formula (18) and following a reaction sequence under suitable conditions analogous to the applicable portion that is described in Scheme 3B, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (20) may be carried out by a process as outlined in Scheme 22B, comprising the steps of starting with compound of formula (22) and following a reaction sequence under suitable conditions analogous to the applicable portion that is described in Scheme 2B, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (24) may be carried out by a process as outlined in Scheme 23B, comprising the steps of starting with compound of formula (26) and following a reaction sequence under suitable

conditions analogous to the applicable portion that is described in Scheme 3B, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure compound of formula (8) may be carried out by a process as outlined in Scheme 24, comprising the steps of starting with compound of formula (1) and following a reaction sequence under suitable conditions analogous to the applicable portion that is described in Scheme 1, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure compound of formula (18) may be carried out by a process as outlined in Scheme 25A, comprising the steps of starting with compound of formula (11) and following a reaction sequence under suitable conditions analogous to the applicable portion that is described in Scheme 2A, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure compound of formula (22) may be carried out by a process as outlined in Scheme 25B, comprising the steps of starting with compound of formula (11) and following a reaction sequence under suitable conditions analogous to the applicable portion that is described in Scheme 2B, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure compound of formula (26) may be carried out by a process as outlined in Scheme 26B, comprising the steps of starting with compound of formula (11) and following a reaction sequence under suitable conditions analogous to the applicable portion that is described in Scheme 3B, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure compound of formula (6) may be carried out by a process as outlined in Scheme 27, comprising the steps of starting with compound of formula (1) and following a reaction sequence under suitable conditions analogous to the applicable portion that is described in Scheme 1, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure compound of formula (16) may be carried out by a process as outlined in Scheme 28A, comprising the steps of starting with compound of formula (11) and following a reaction sequence under suitable conditions analogous to the applicable portion that is described in Scheme 2A, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure compound of formula (5) may be carried out by a process as outlined in Scheme 29, comprising the steps of starting with compound of formula (1) and following a reaction sequence under suitable conditions analogous to the applicable portion that is described in Scheme 1, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure compound of formula (15) may be carried out by a process as outlined in Scheme 30A, comprising the steps of starting with compound of formula (11) and following a reaction sequence under suitable conditions analogous to the applicable portion that is described in Scheme 2A, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure compound of formula (4) may be carried out by a process as outlined in Scheme 31, comprising the steps of starting with compound of formula (1) and following a reaction sequence under suitable conditions analogous to the applicable portion that is described in Scheme 1, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure compound of formula (14) may be carried out by a process as outlined in Scheme 32A, comprising the steps of starting with compound of formula (11) and following a reaction sequence under suitable conditions analogous to the applicable portion that is described in Scheme 2A, wherein all the formulae and symbols are as described above.

In another aspect, the present invention provides a compound of formula (4), or a solvate or pharmaceutically acceptable salt thereof; wherein all the formulae and symbols are as described above.

In another aspect, the present invention provides a compound of formula (5), or a solvate or pharmaceutically acceptable salt thereof; wherein all the formulae and symbols are as described above.

In another aspect, the present invention provides a compound of formula (6), or a solvate or pharmaceutically acceptable salt thereof; wherein all the formulae and symbols are as described above.

In another aspect, the present invention provides a compound of formula (7), or a solvate or pharmaceutically acceptable salt thereof; wherein all the formulae and symbols are as described above with the proviso that  $R_3$ ,  $R_4$  and  $R_5$  cannot all be hydrogen.

In another aspect, the present invention provides a compound of formula (8), or a solvate or pharmaceutically acceptable salt thereof; wherein all the formulae and symbols are as described above with the proviso that when  $R_3$ ,  $R_4$  and  $R_5$  are all hydrogen then J is not a methanesulfonyl group.

In another aspect, the present invention provides a compound of formula (14), or a solvate or pharmaceutically acceptable salt thereof; wherein all the formulae and symbols are as described above.

In another aspect, the present invention provides a compound of formula (15), or a solvate or pharmaceutically acceptable salt thereof; wherein all the formulae and symbols are as described above.

In another aspect, the present invention provides a compound of formula (16), or a solvate or pharmaceutically acceptable salt thereof; wherein all the formulae and symbols are as described above.

In another aspect, the present invention provides a compound of formula (17), or a solvate or pharmaceutically acceptable salt thereof; wherein all the formulae and symbols are as described above.

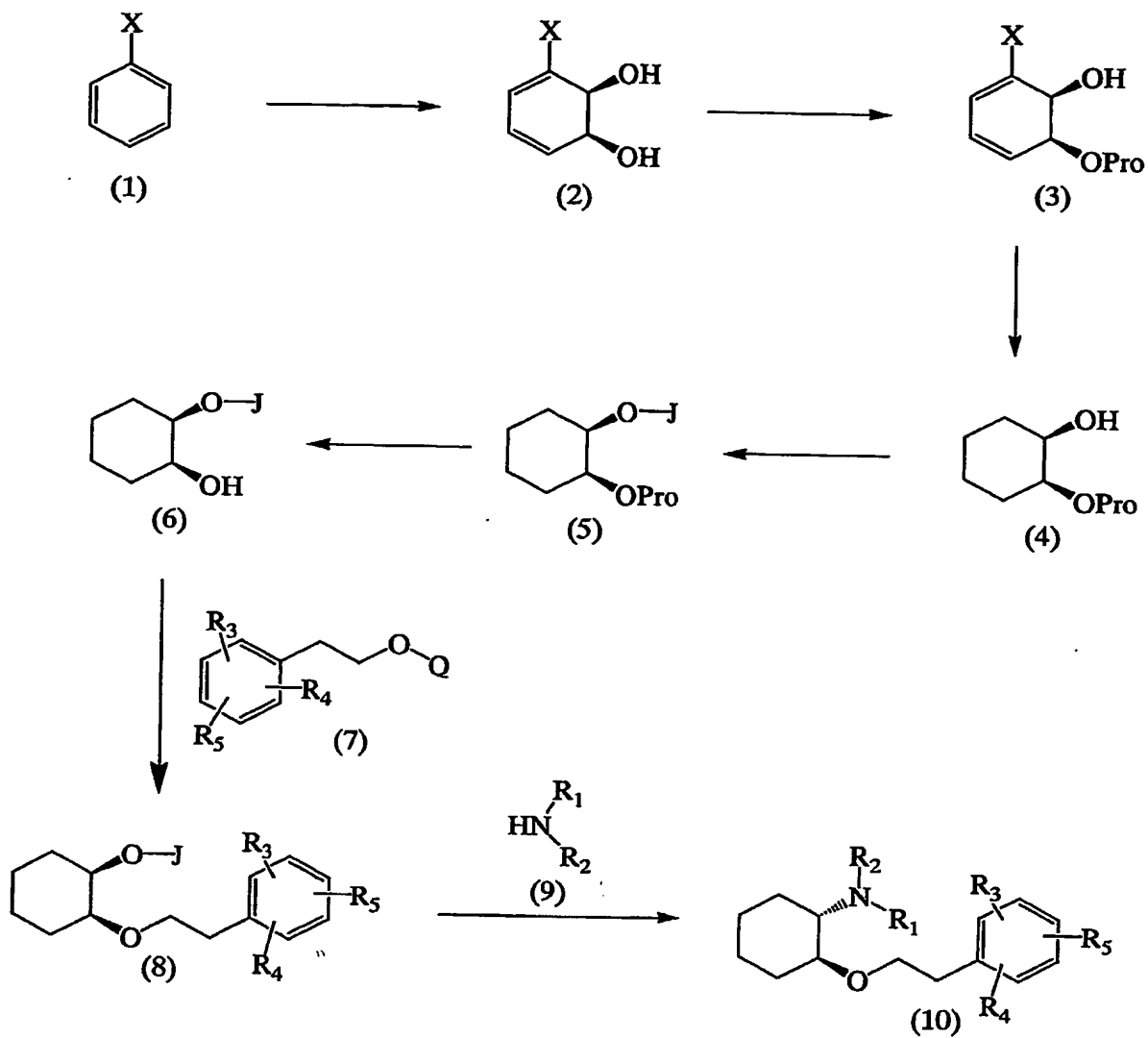
In another aspect, the present invention provides a compound of formula (18), or a solvate or pharmaceutically acceptable salt thereof; wherein all the formulae and symbols are as described above.

In another aspect, the present invention provides a compound of formula (22), or a solvate or pharmaceutically acceptable salt thereof; wherein all the formulae and symbols are as described above.

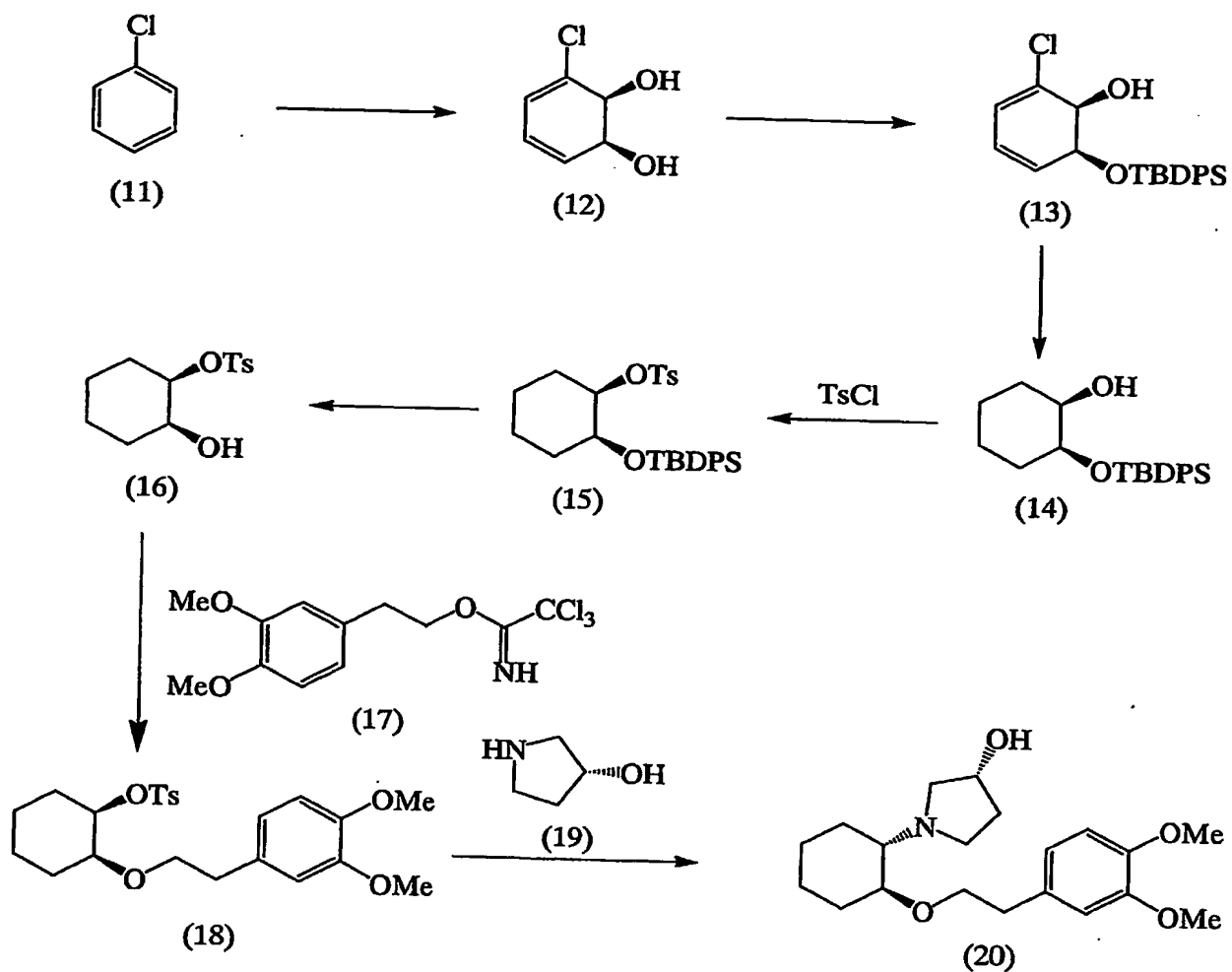
In another aspect, the present invention provides a compound of formula (26), or a solvate or pharmaceutically acceptable salt thereof; wherein all the formulae and symbols are as described above.



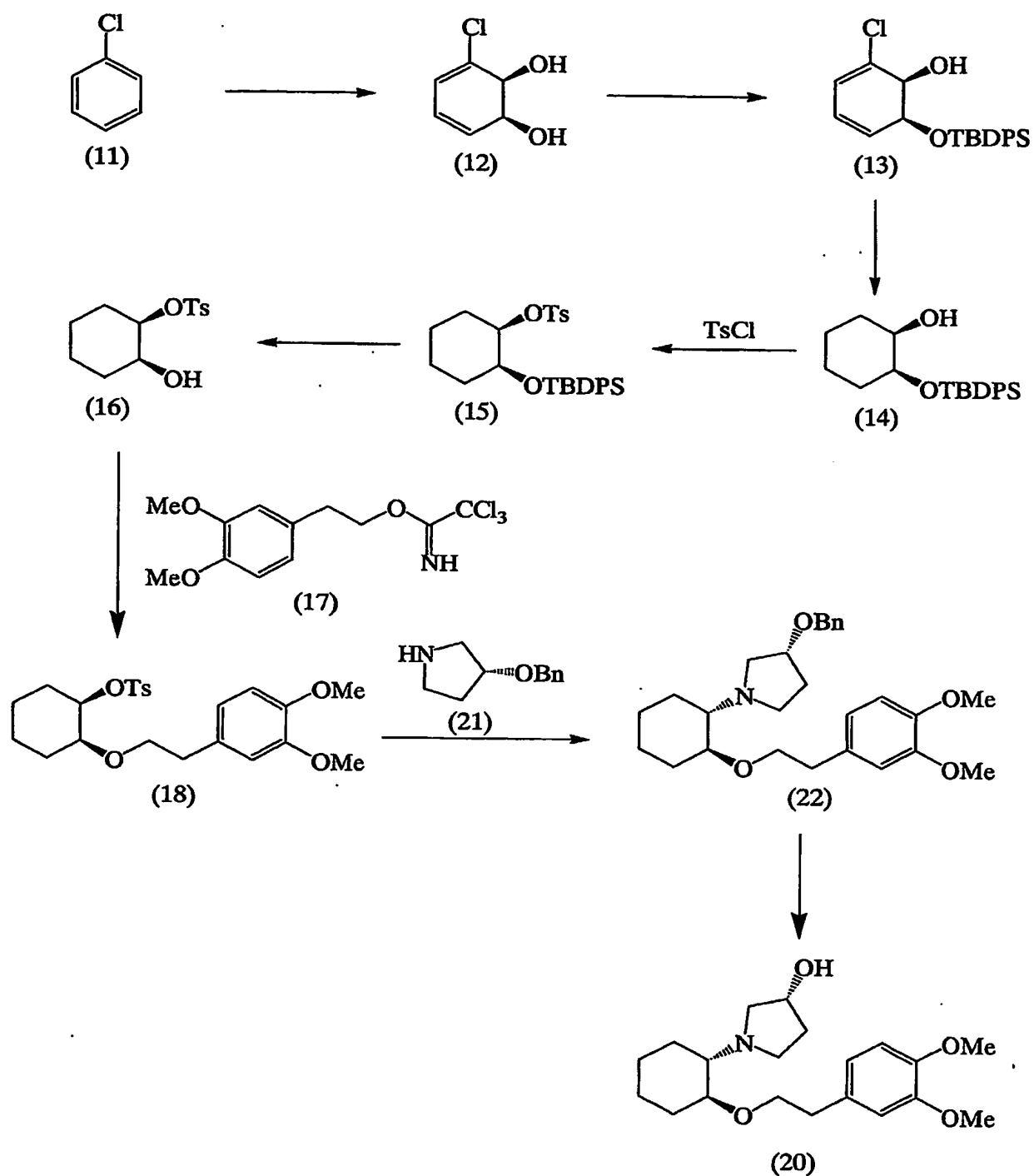
Scheme 1



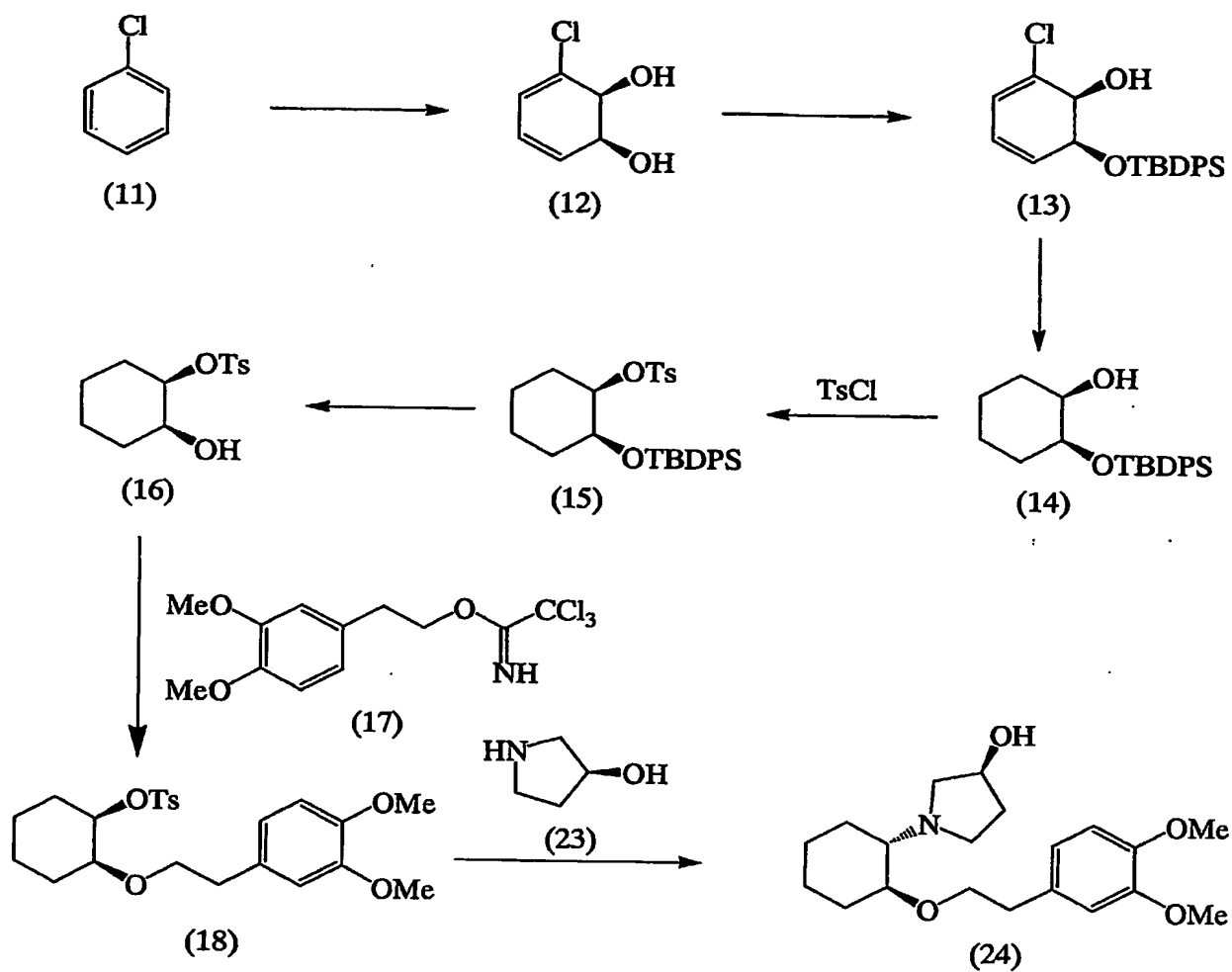
## Scheme 2A



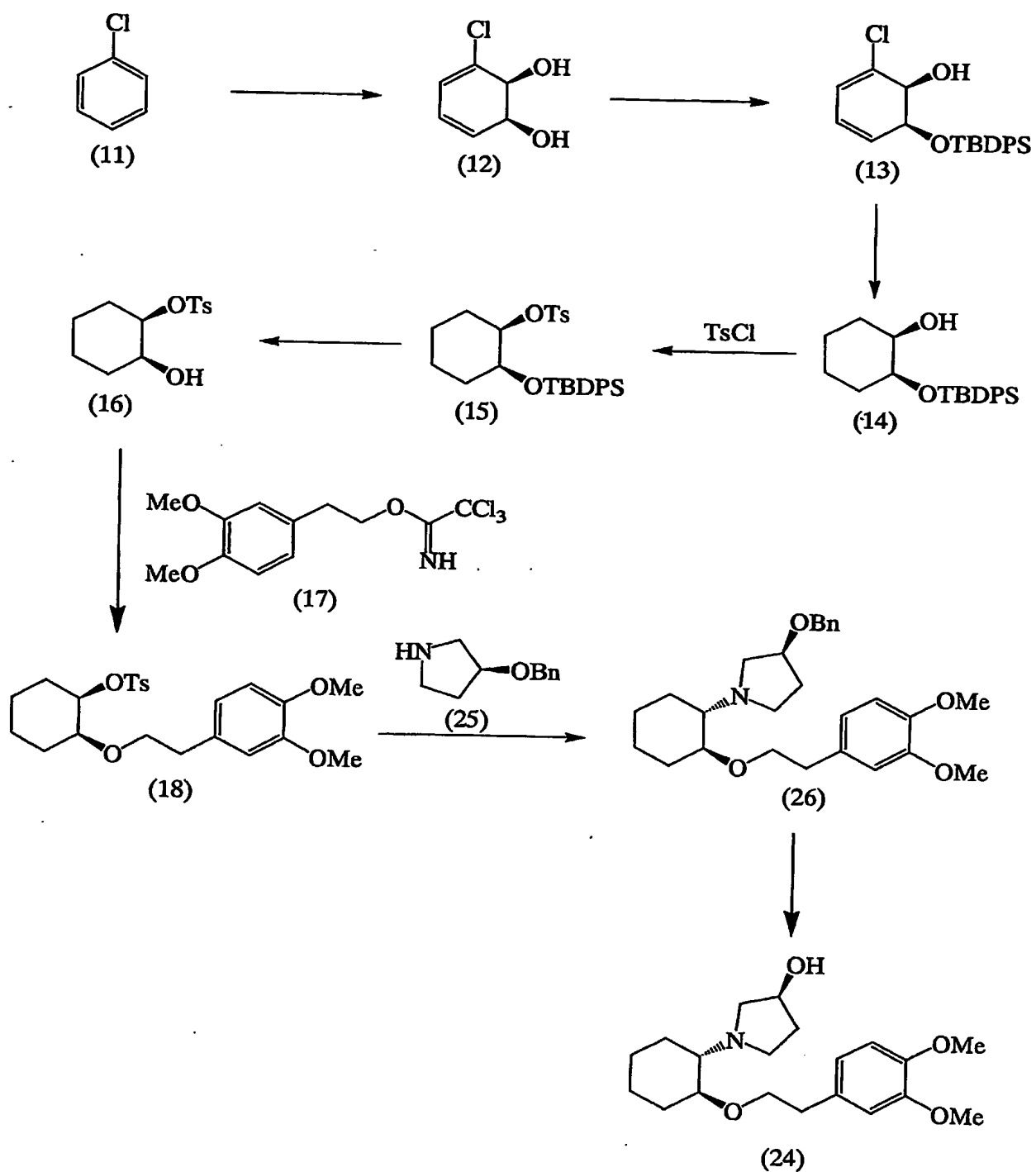
Scheme 2B



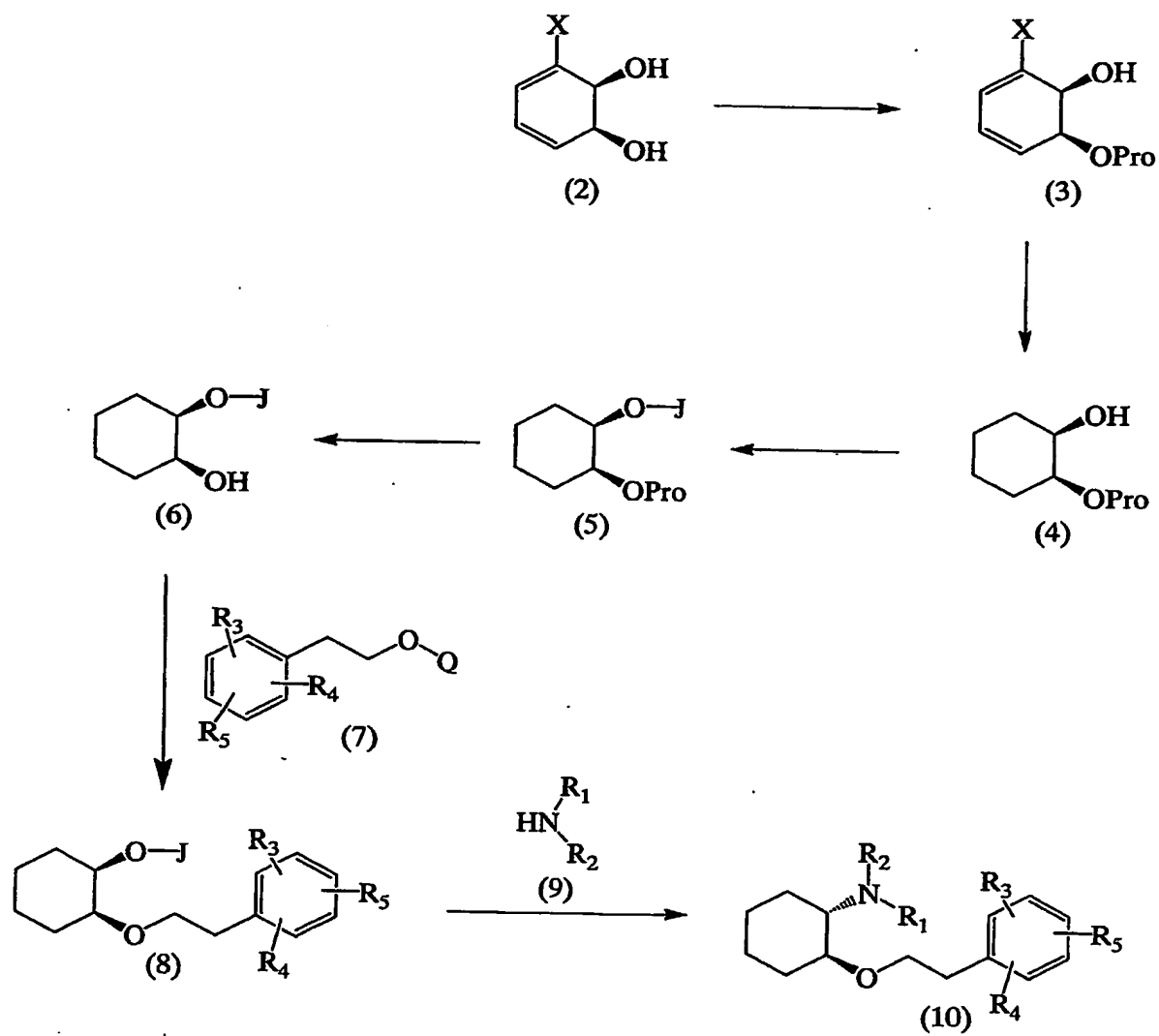
Scheme 3A



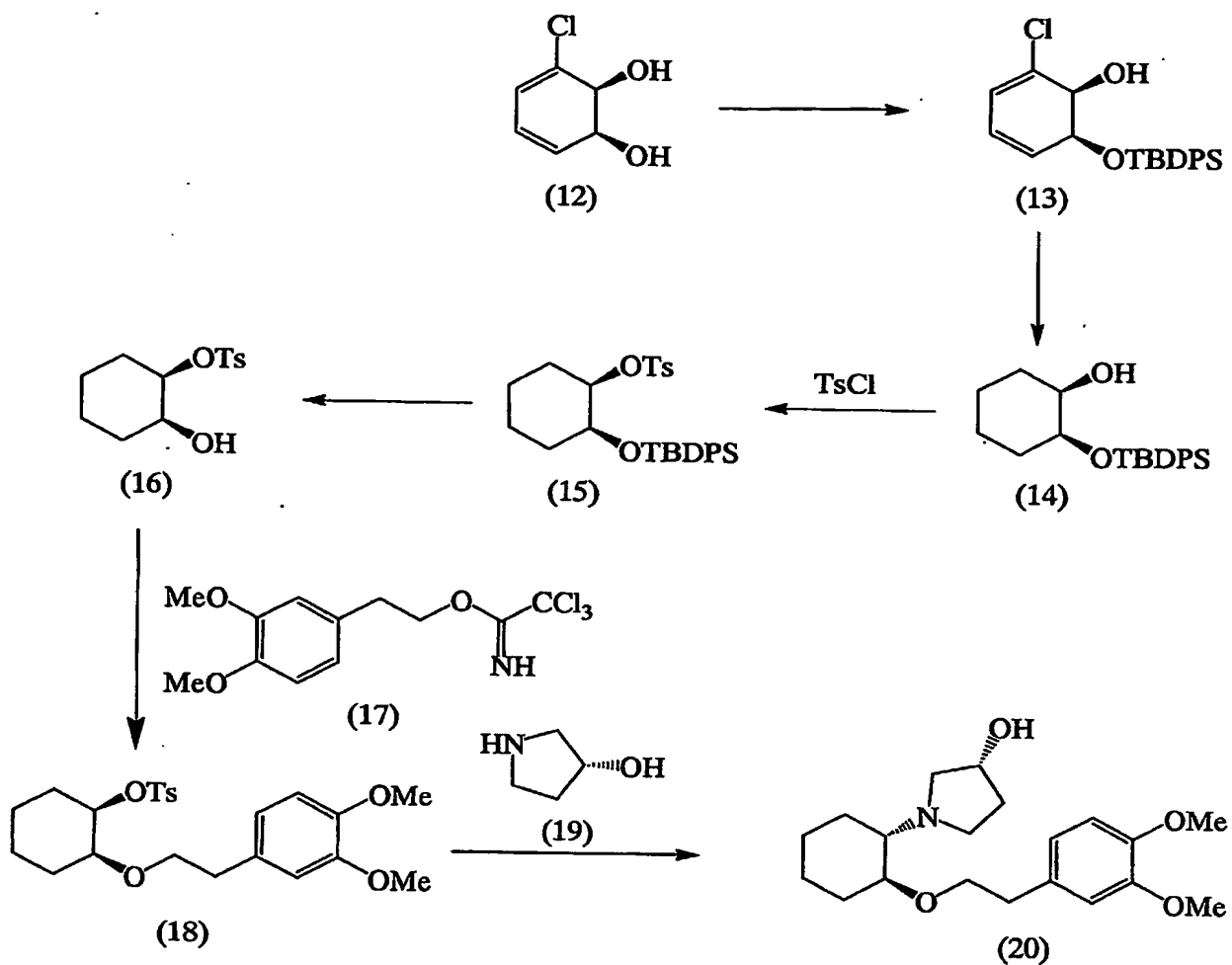
Scheme 3B



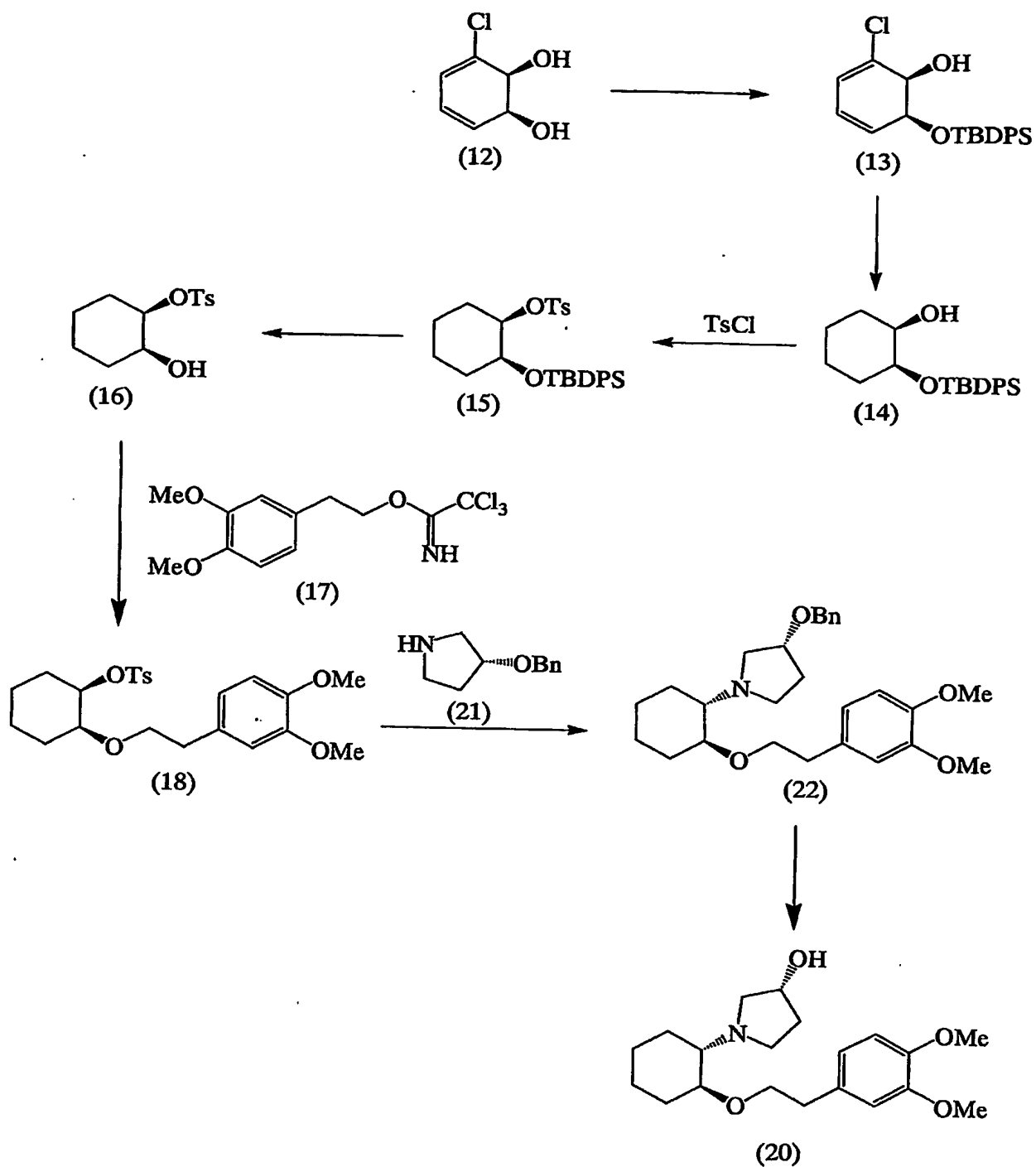
Scheme 4



Scheme 5A

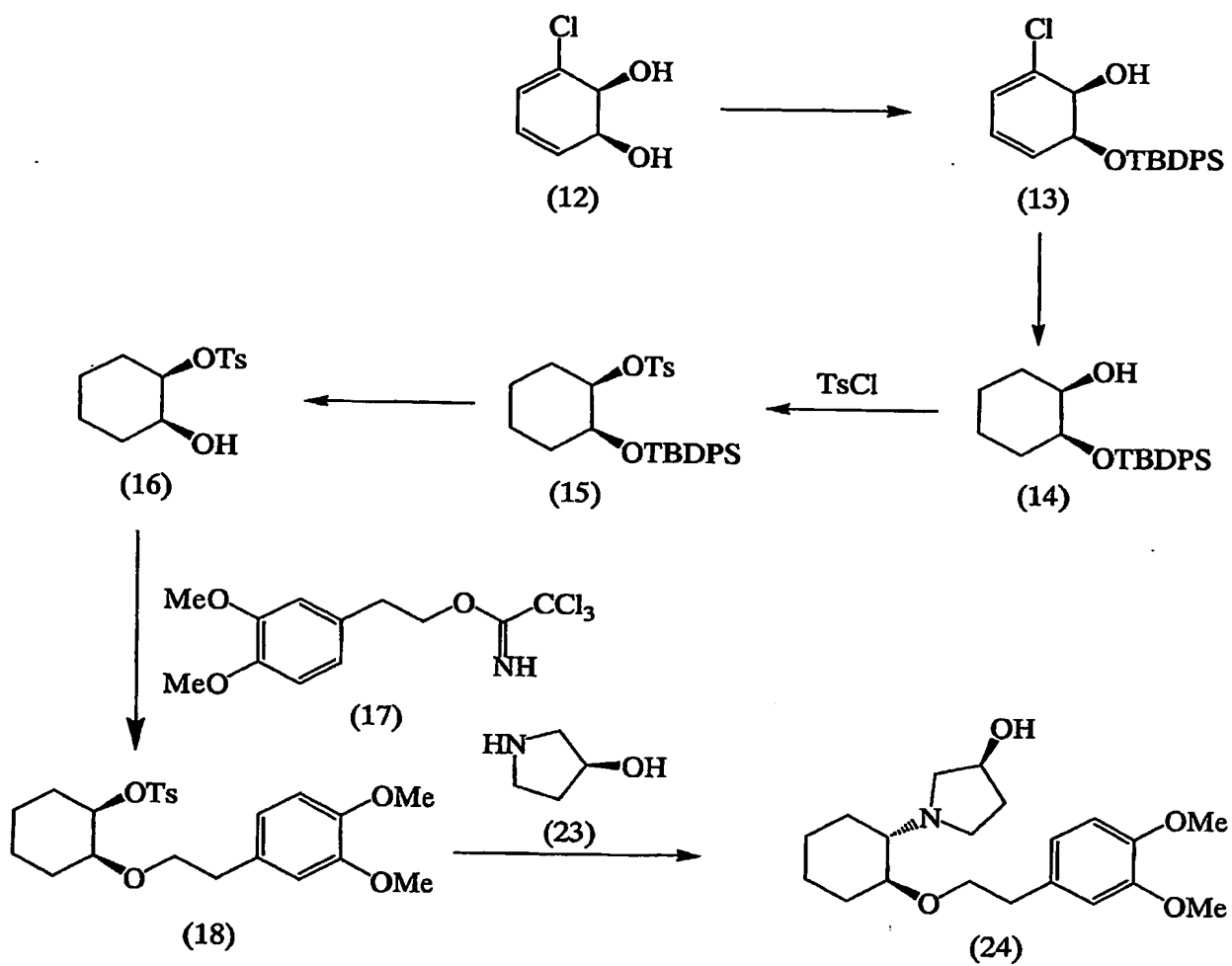


## Scheme 5B

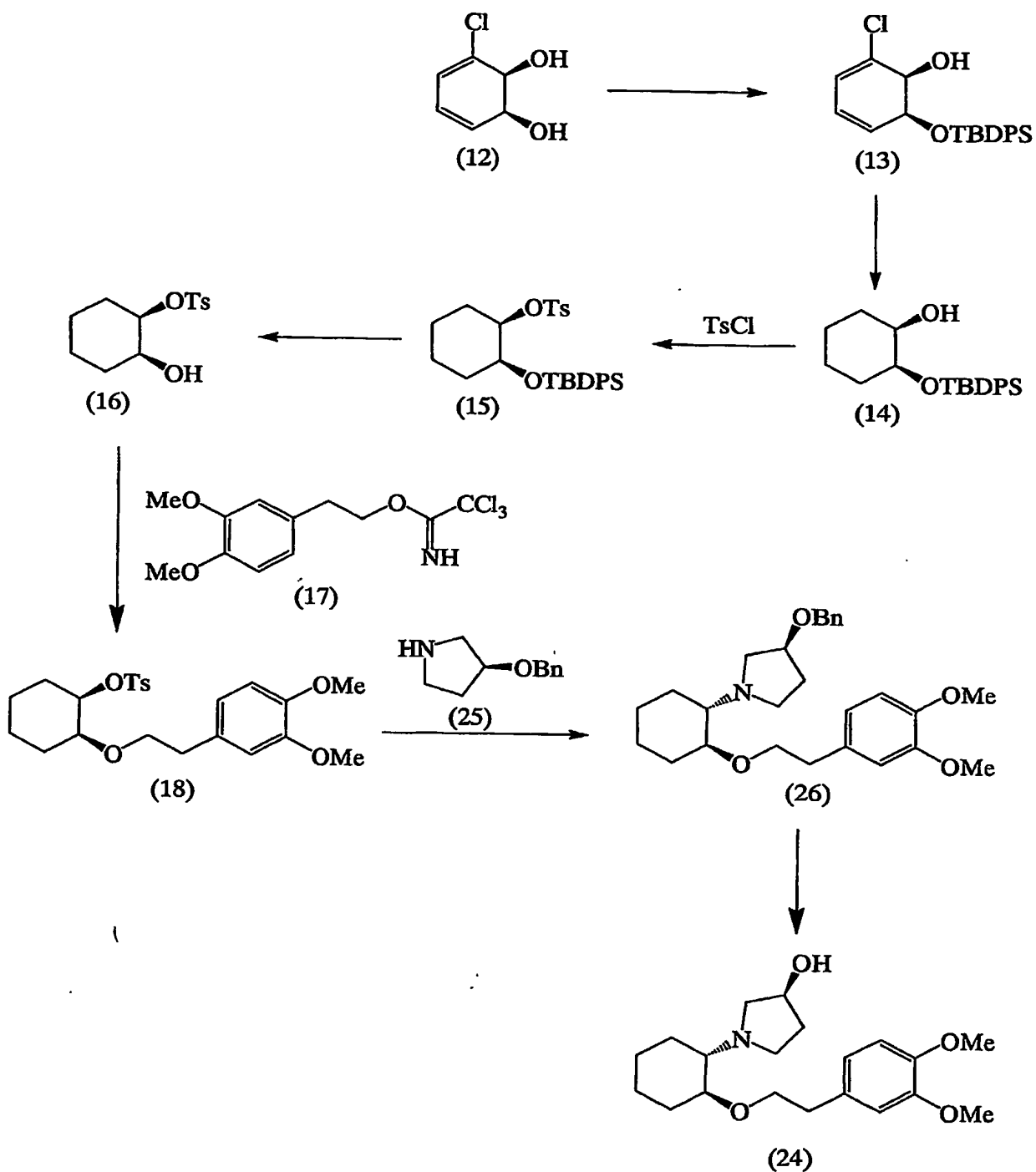




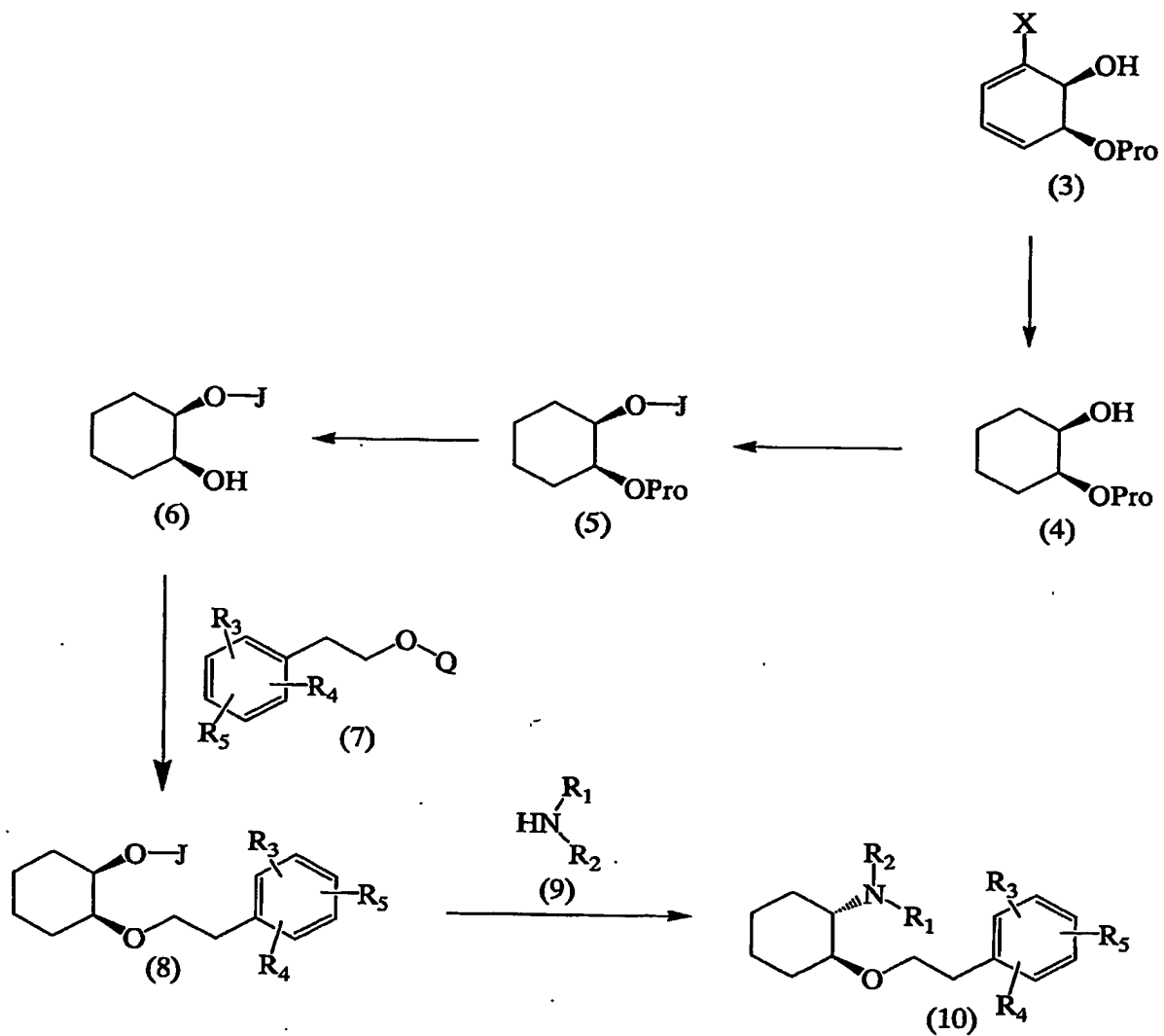
Scheme 6A



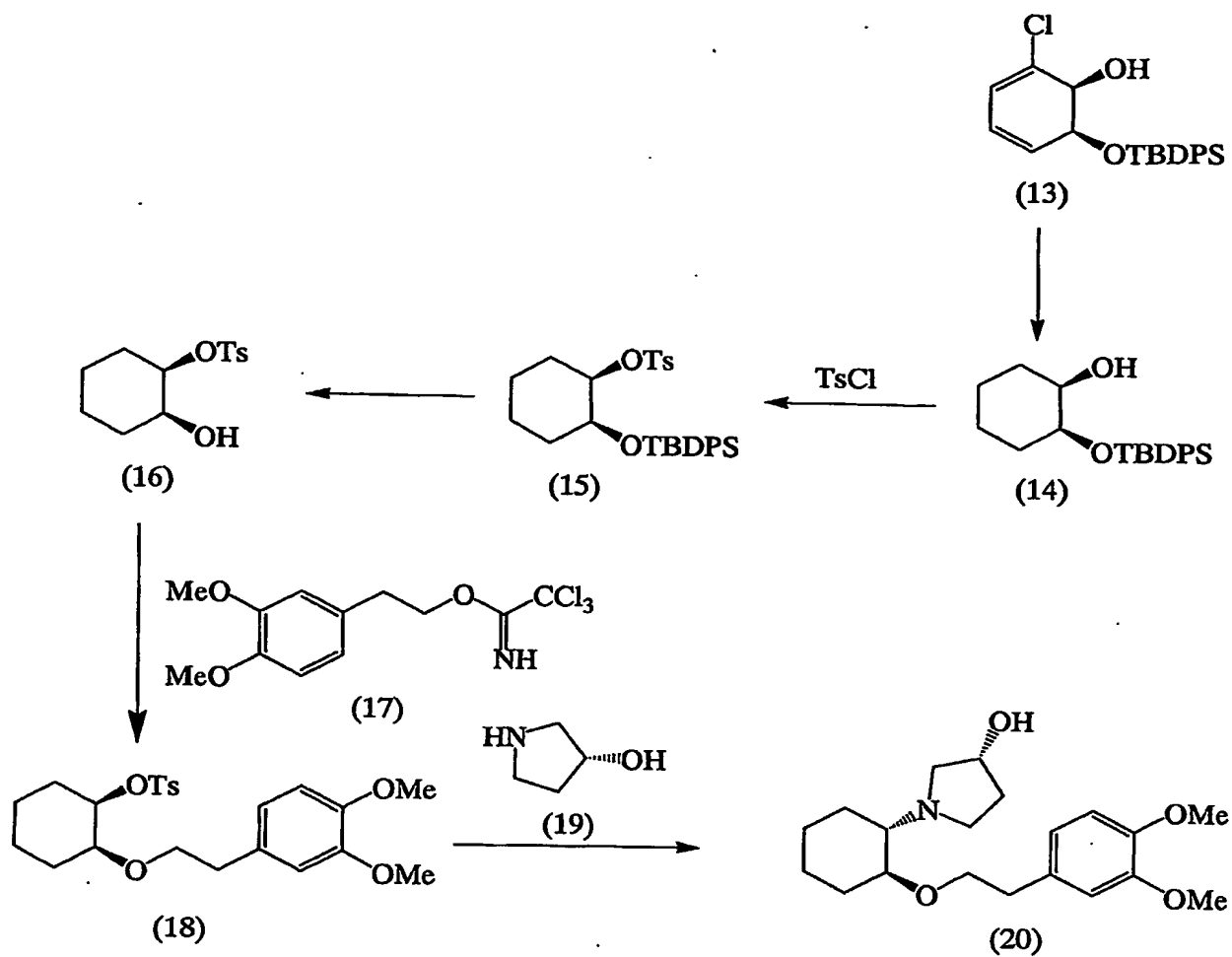
Scheme 6B



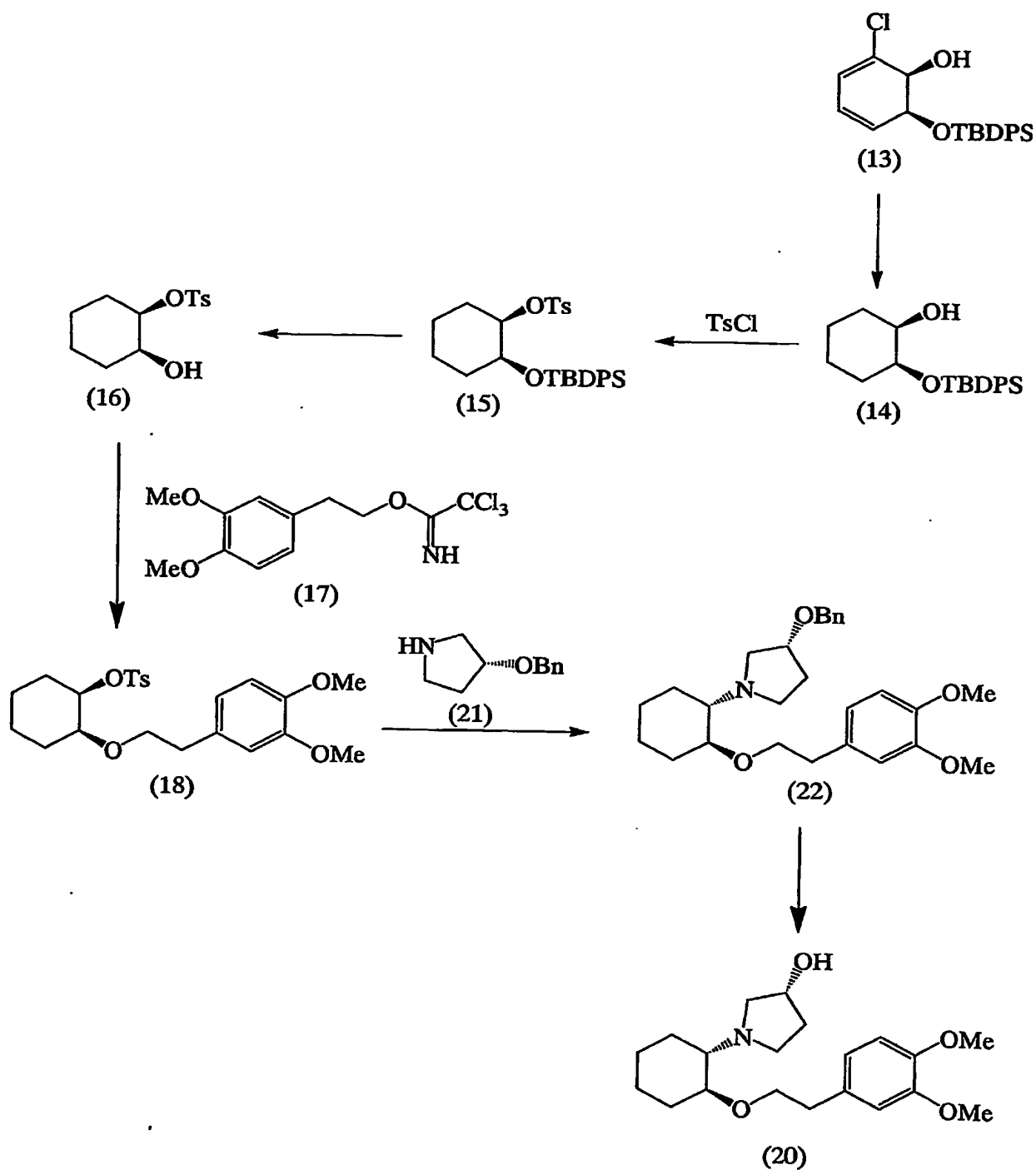
Scheme 7



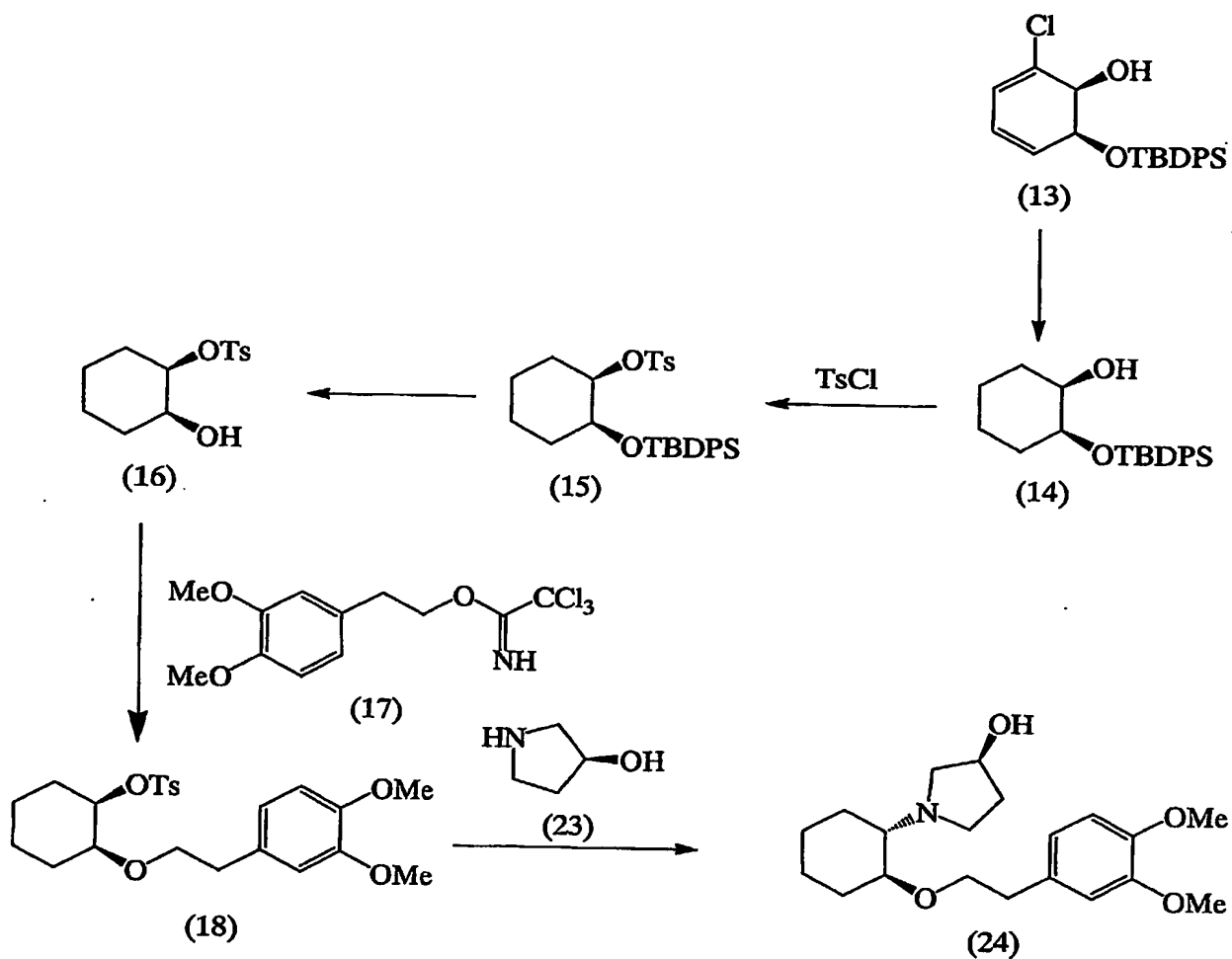
Scheme 8A



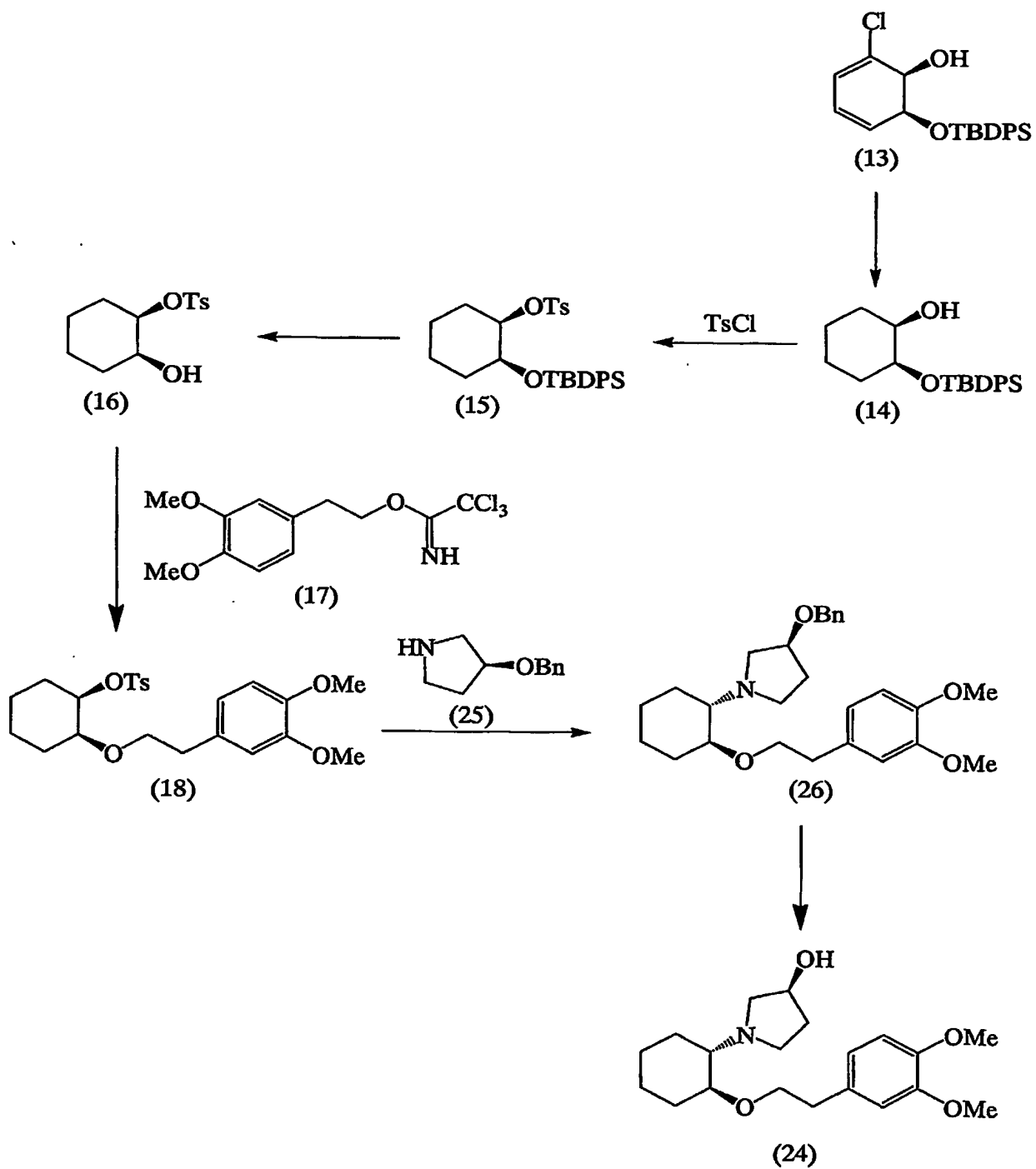
Scheme 8B



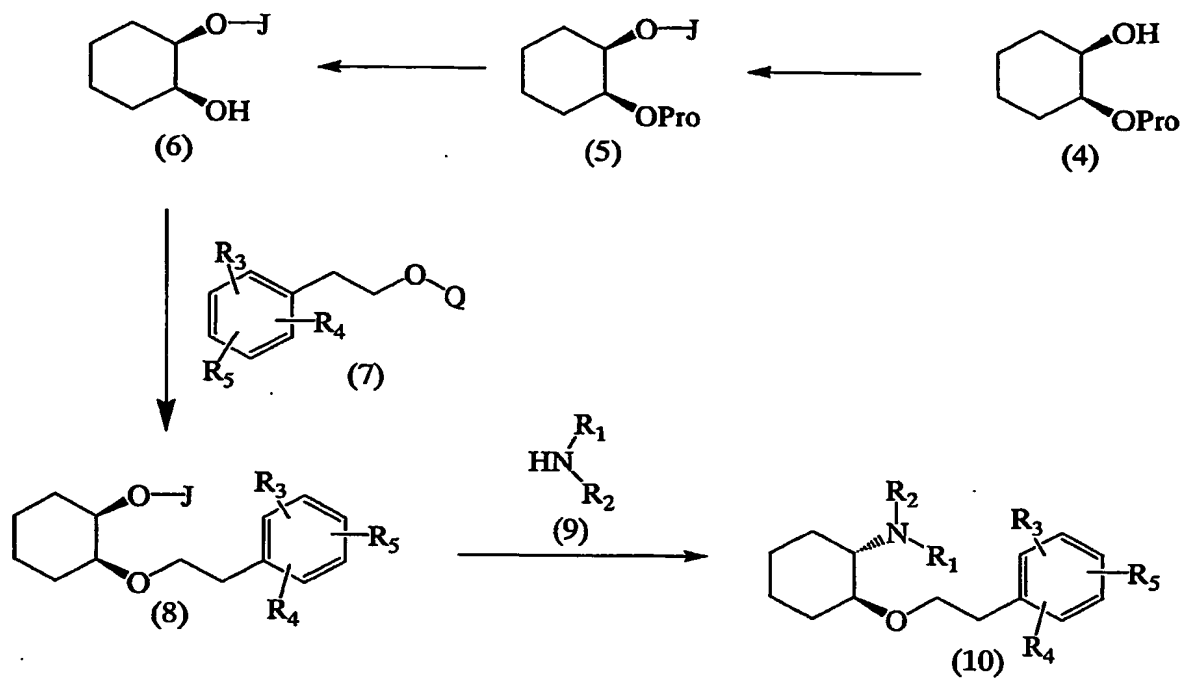
**Scheme 9A**



Scheme 9B

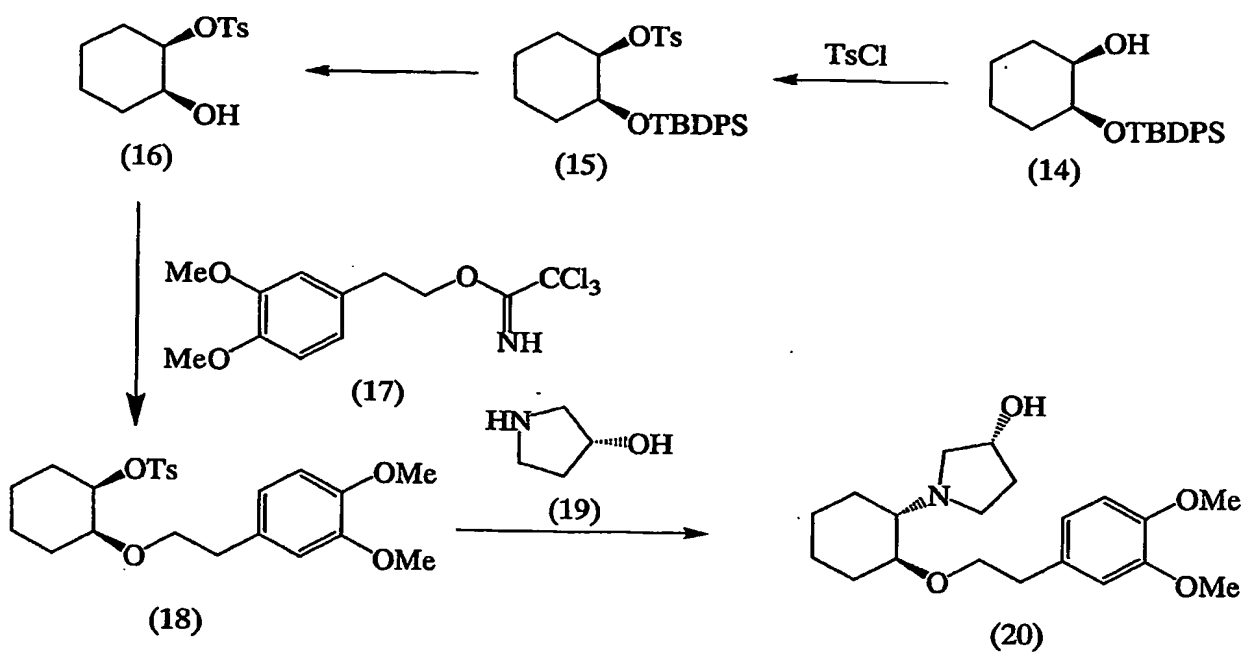


Scheme 10

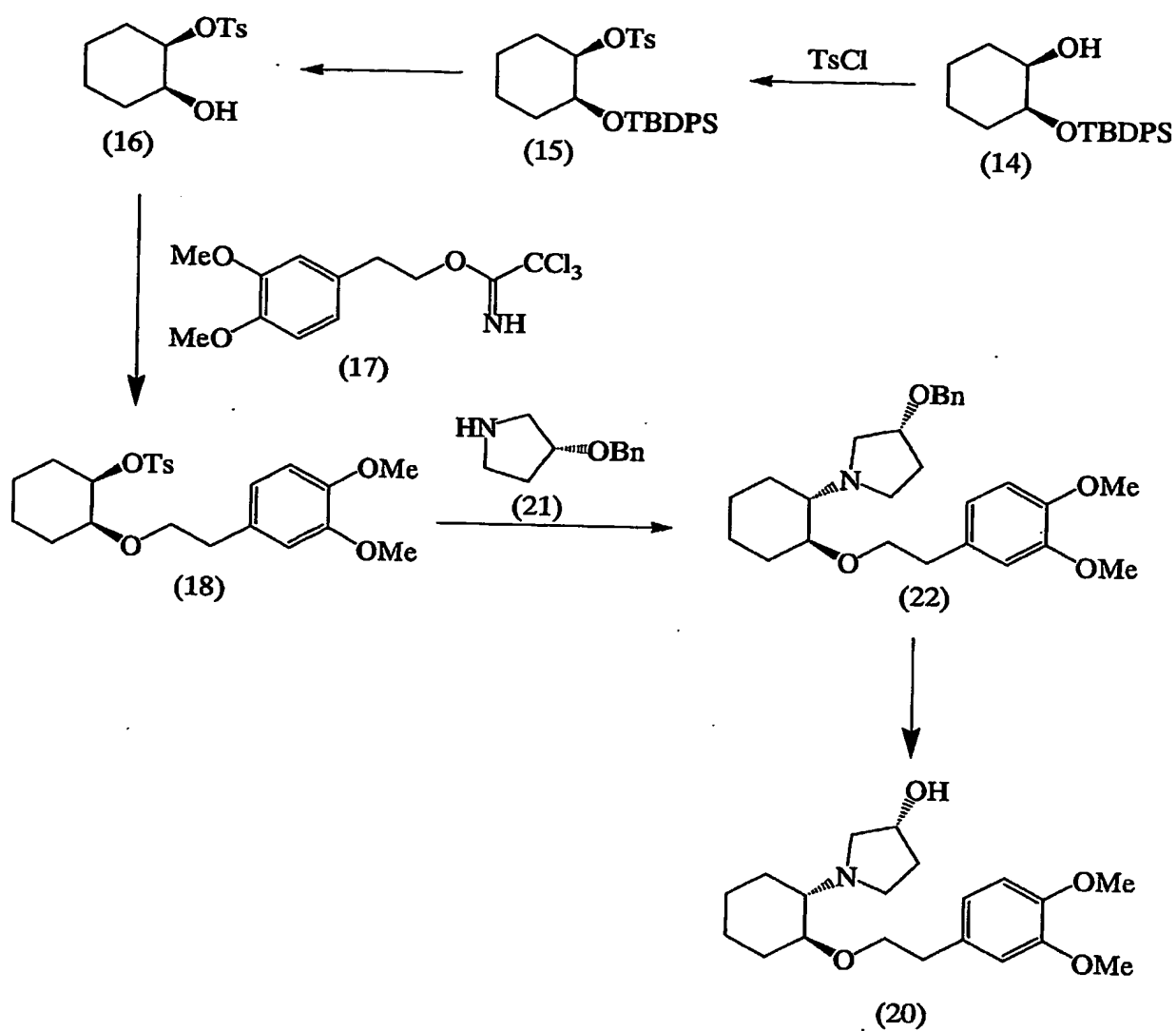




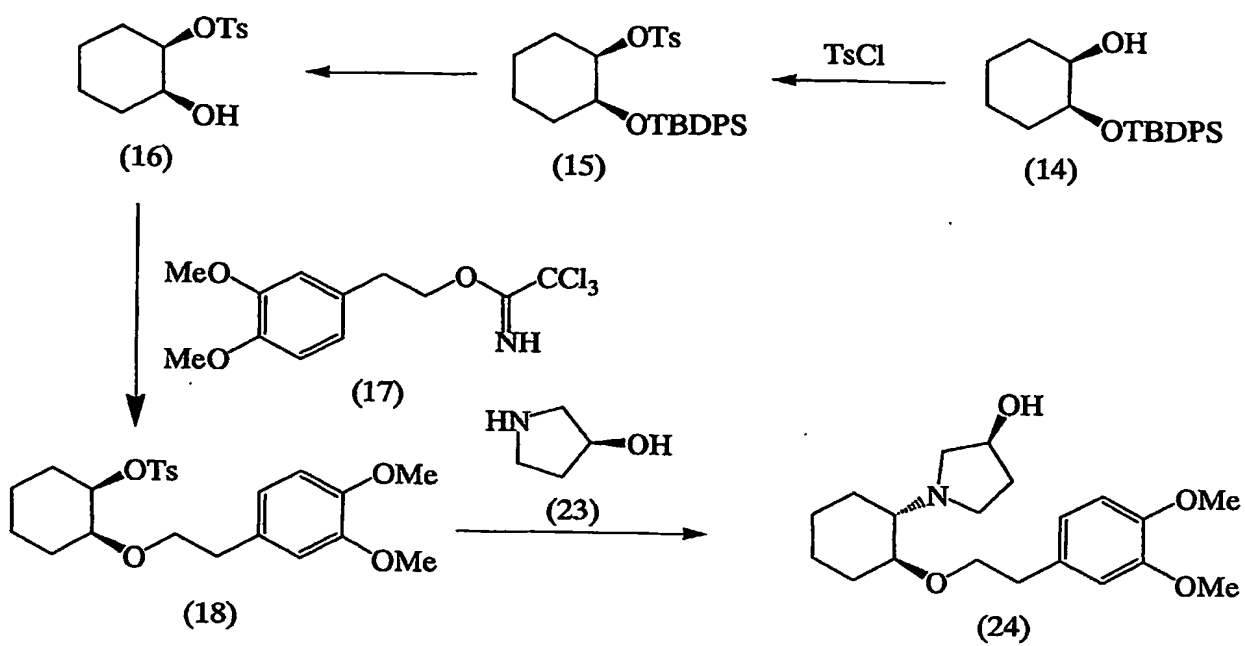
Scheme 11A



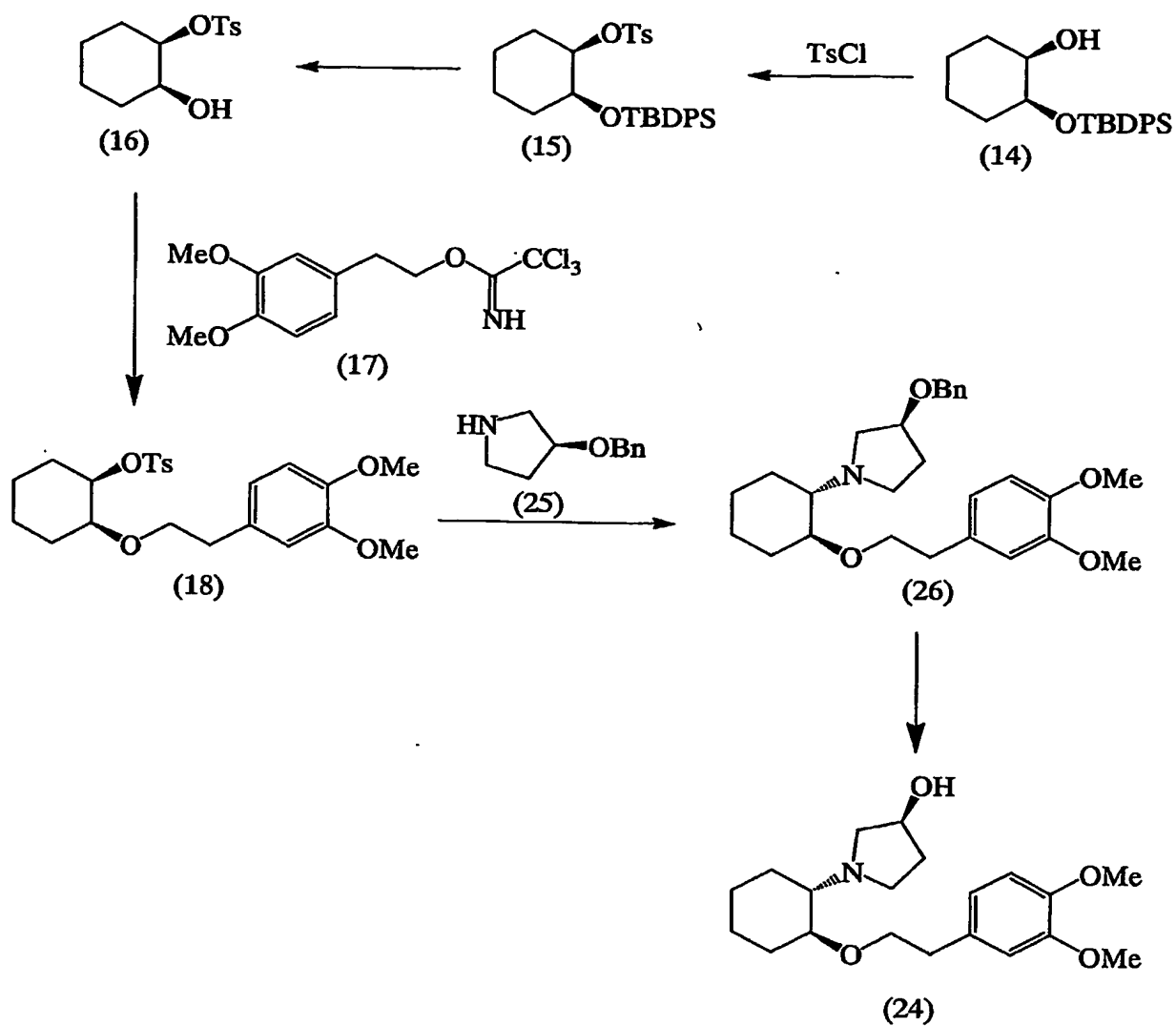
Scheme 11B



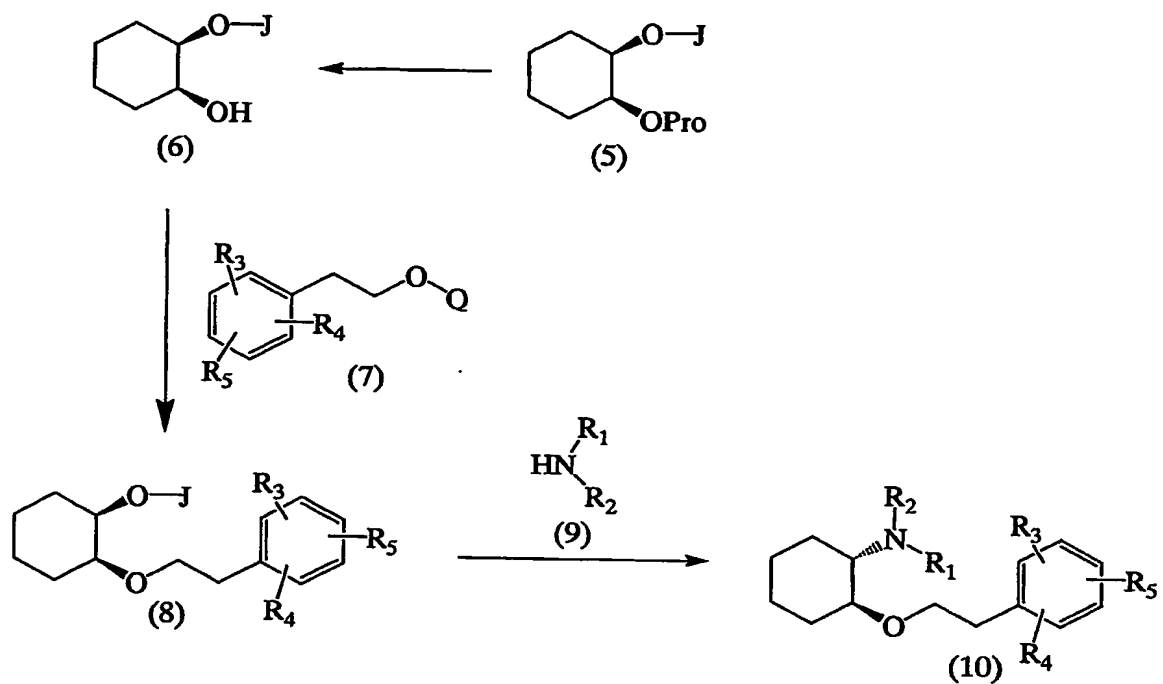
Scheme 12A

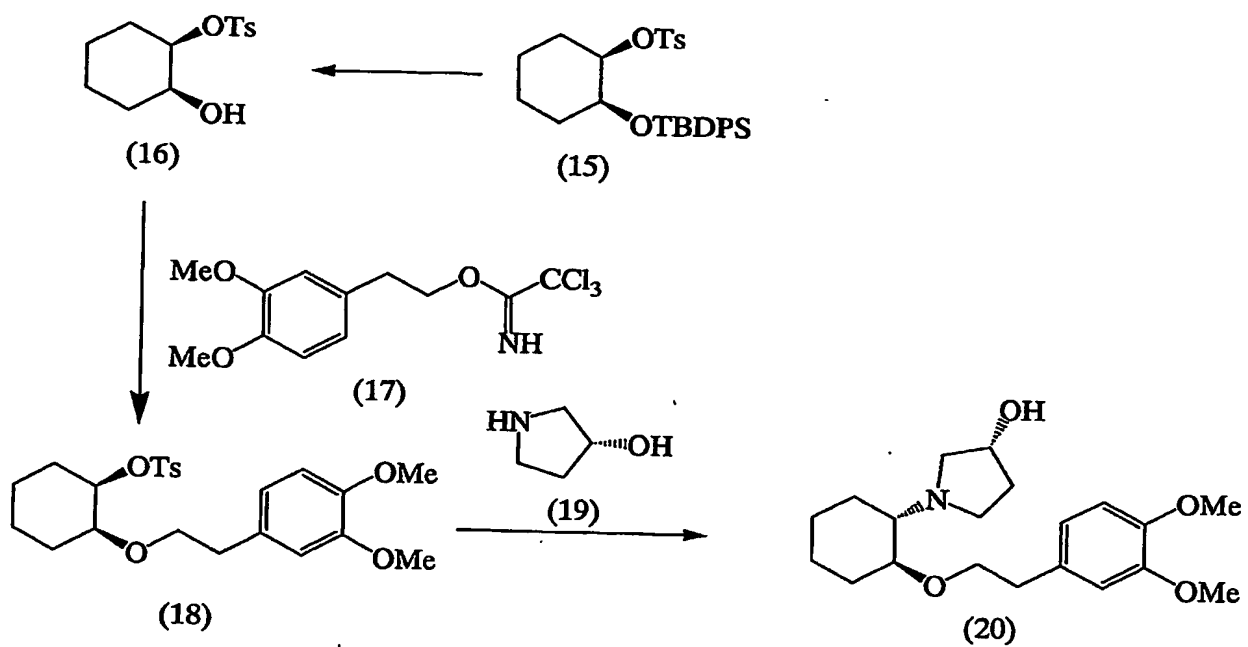


Scheme 12B

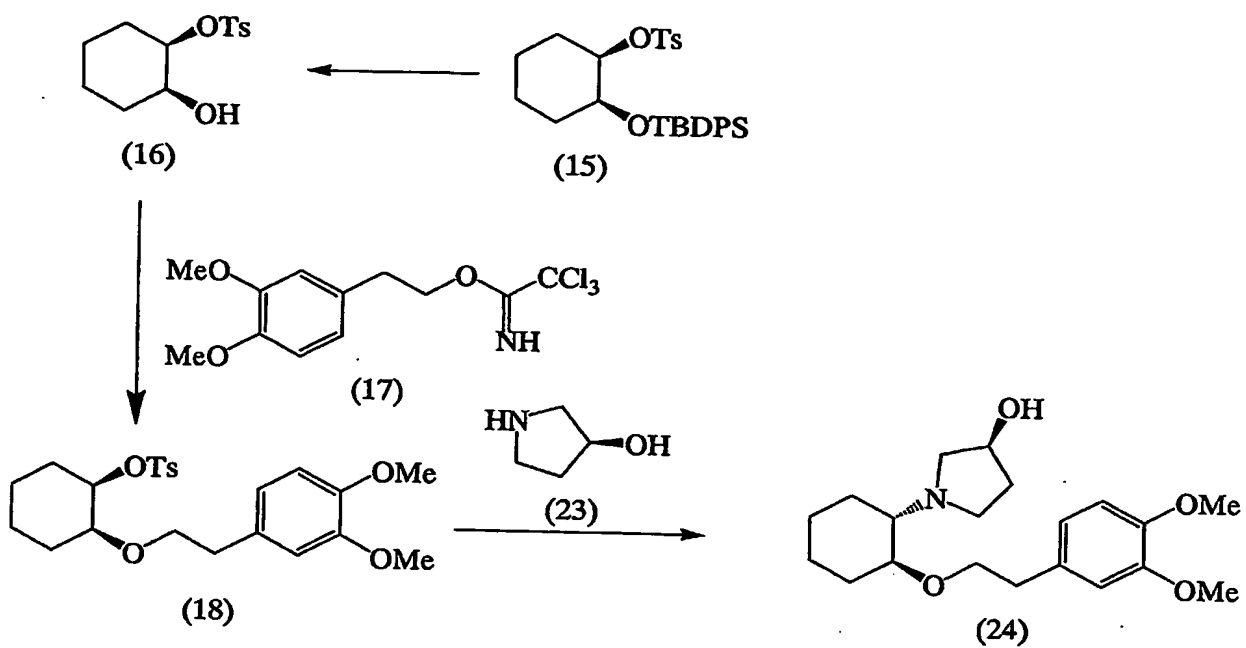


Scheme 13



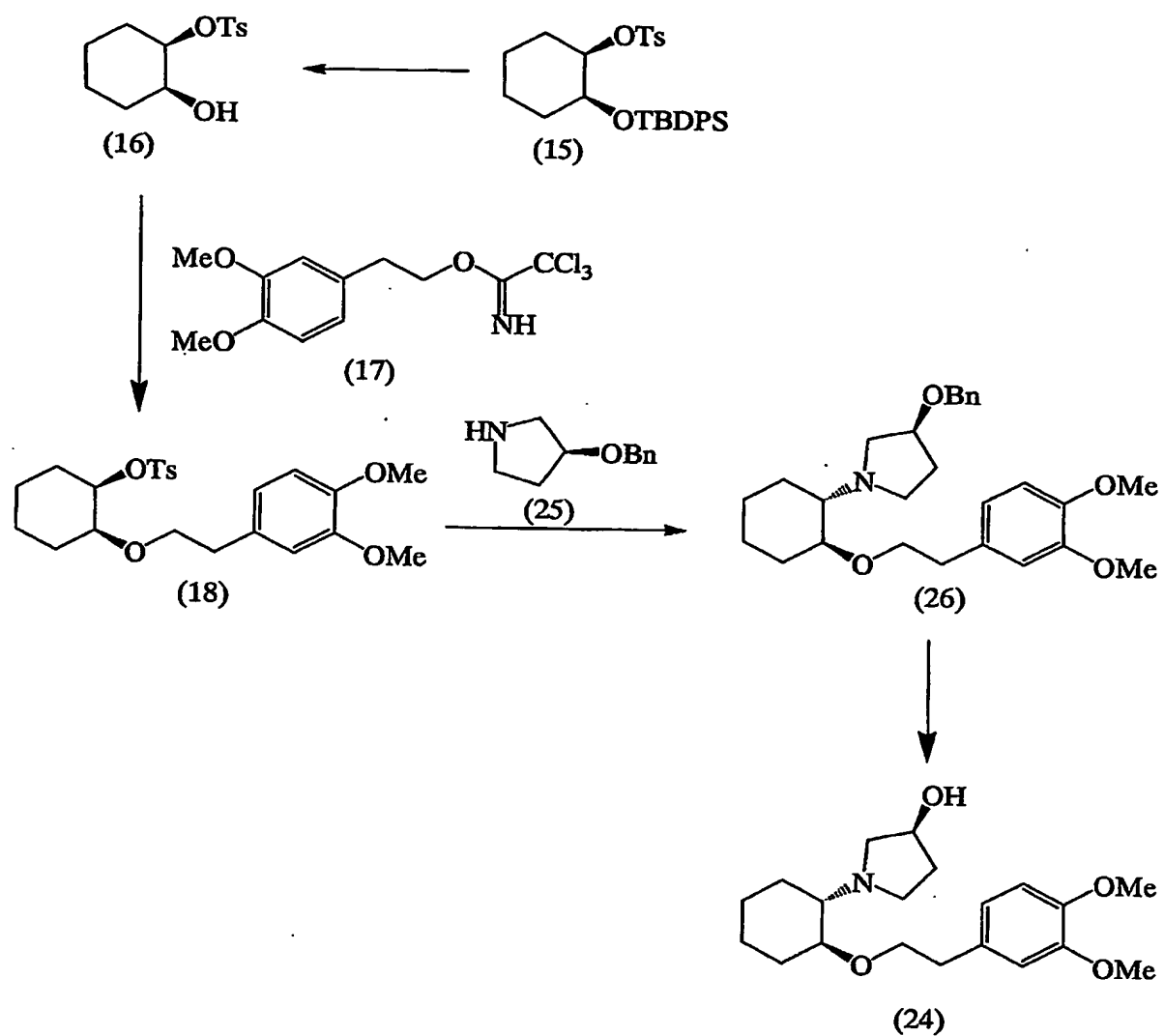
Scheme 14A



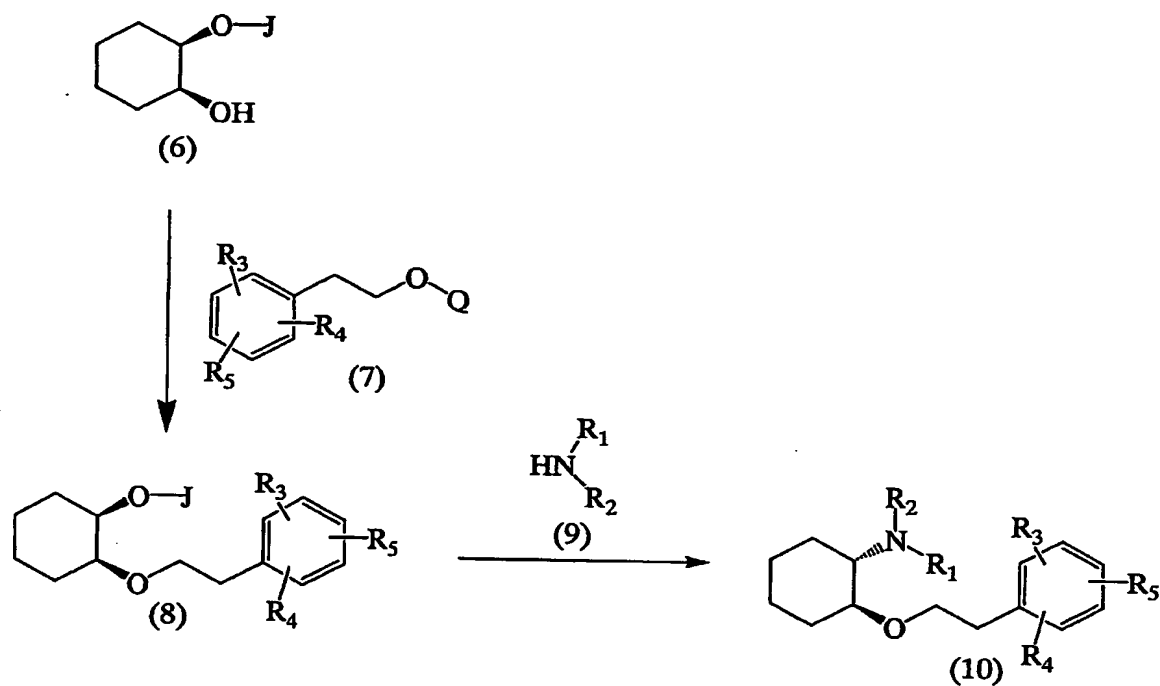
Scheme 15A

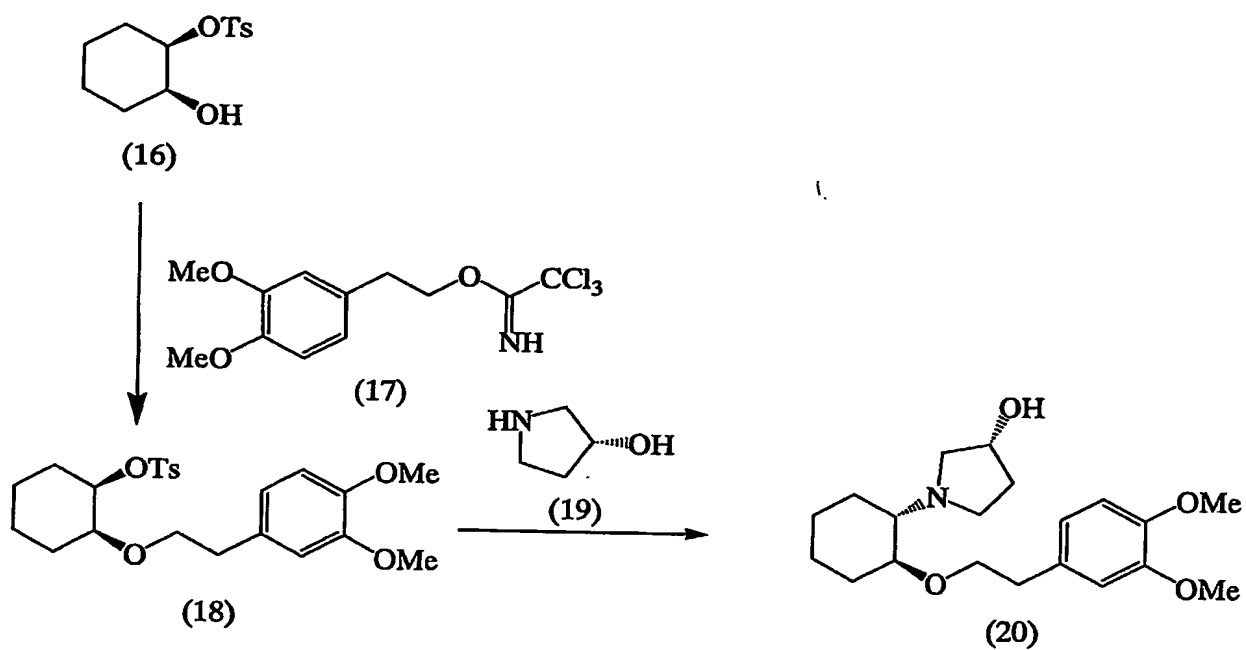


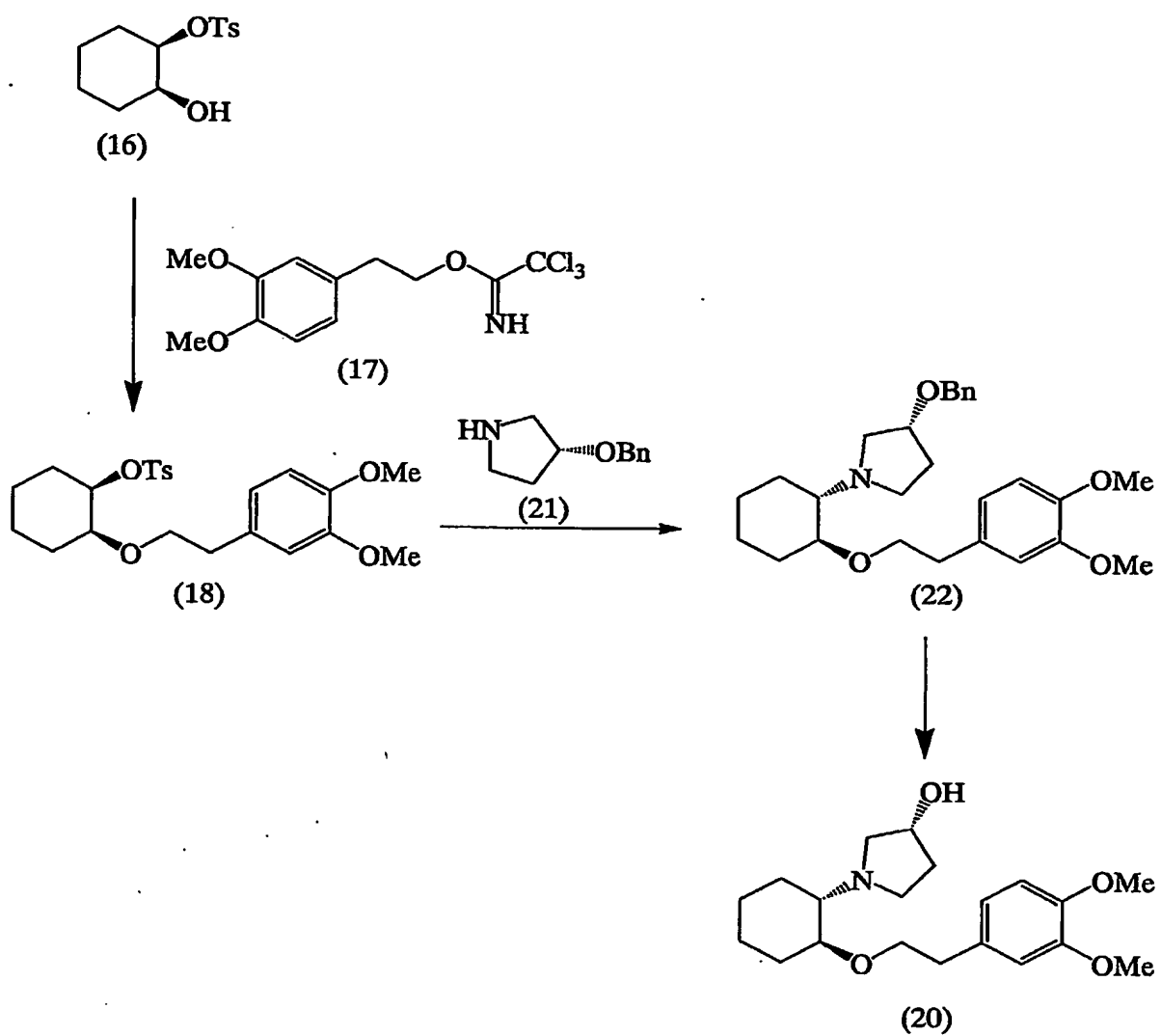
Scheme 15B



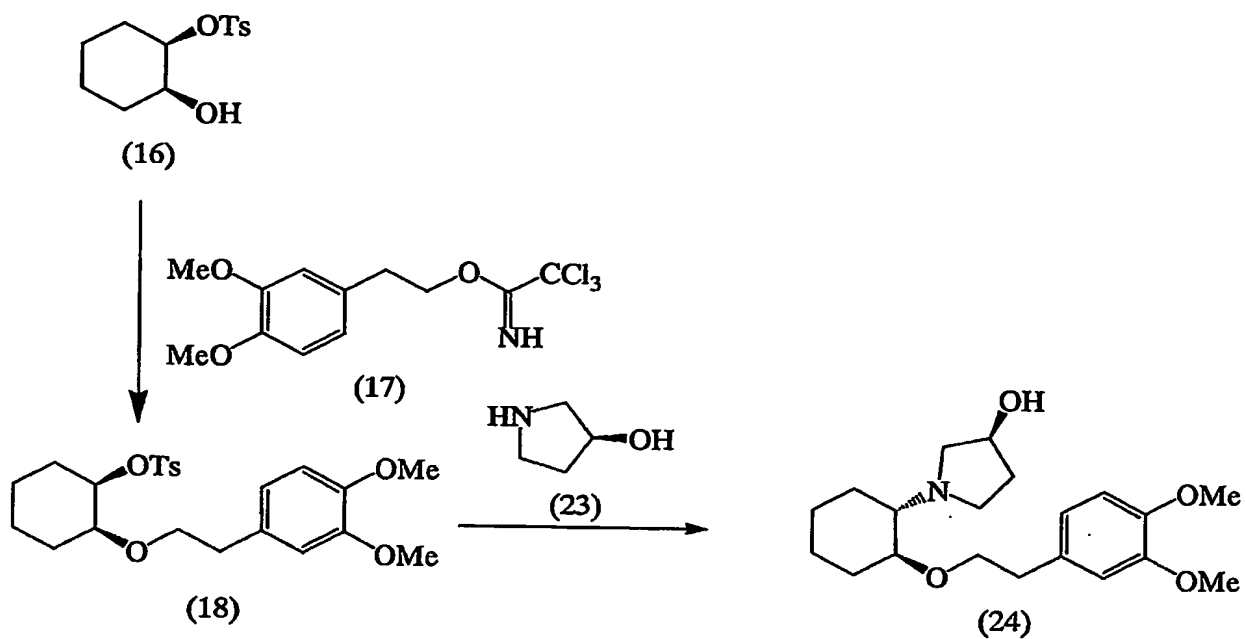
Scheme 16

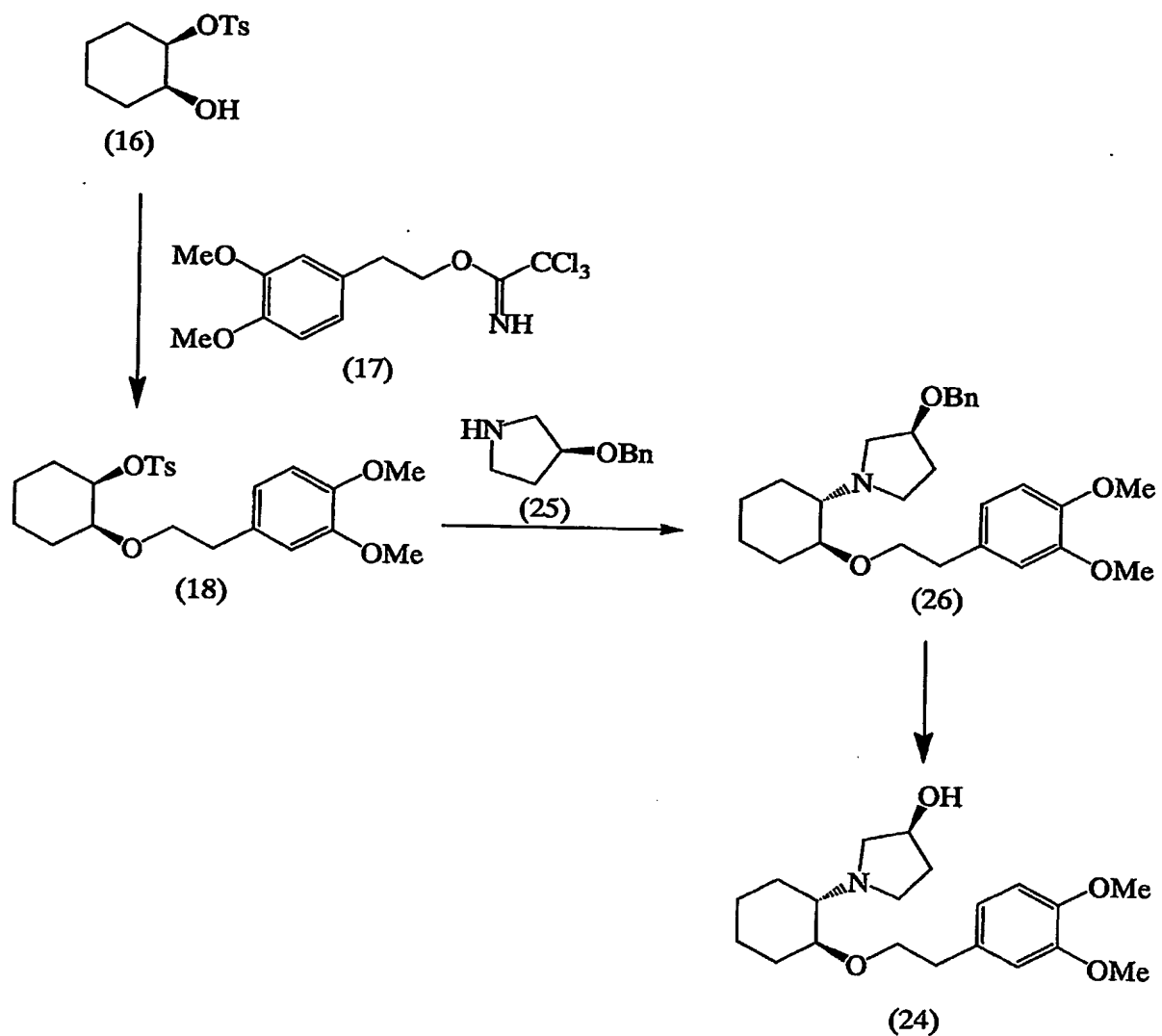


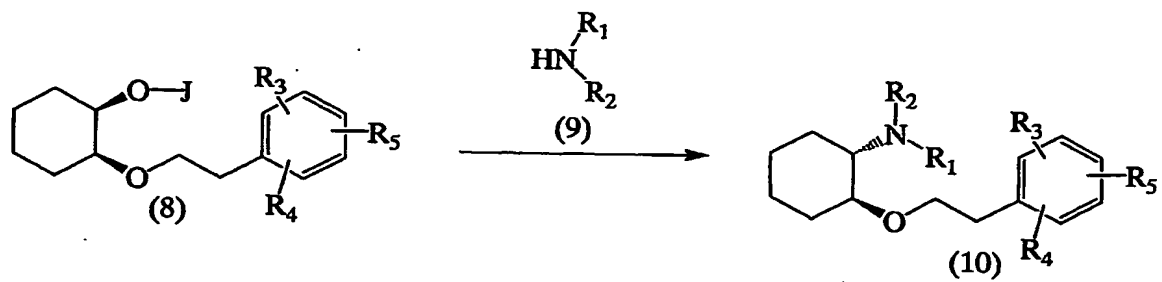
Scheme 17A

Scheme 17B

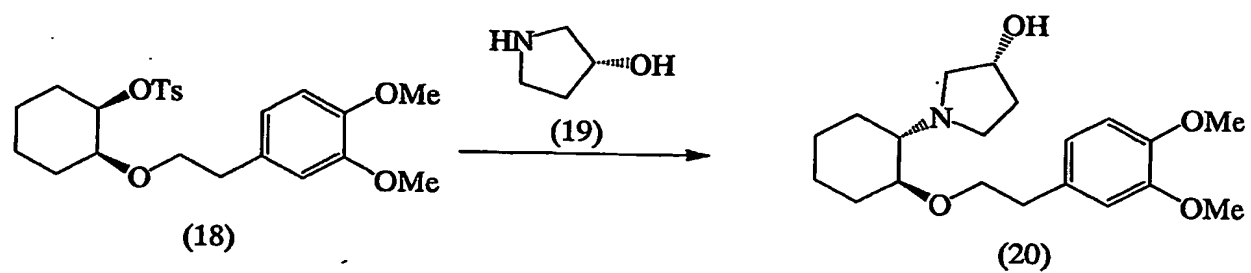
Scheme 18A



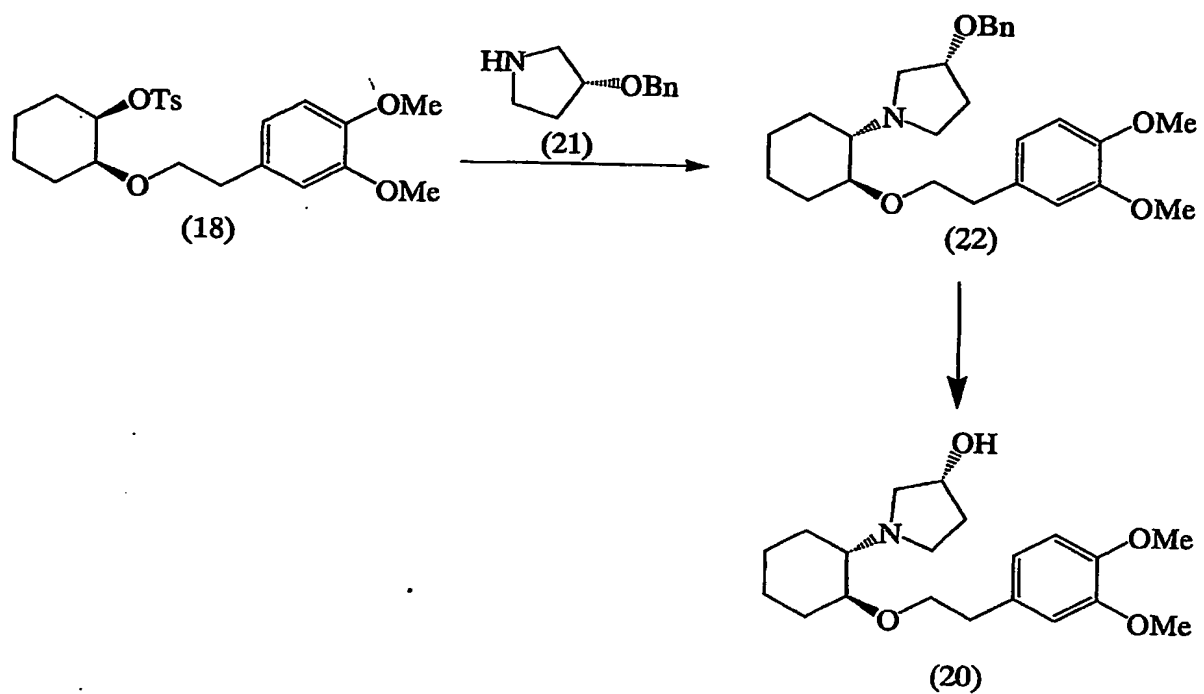
Scheme 18B

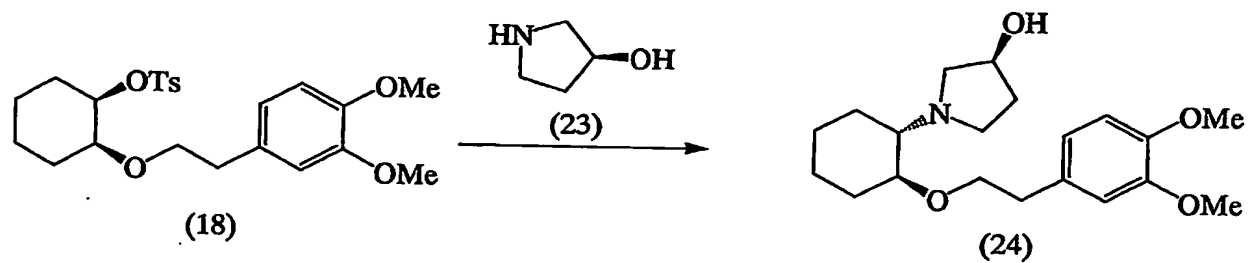
Scheme 19

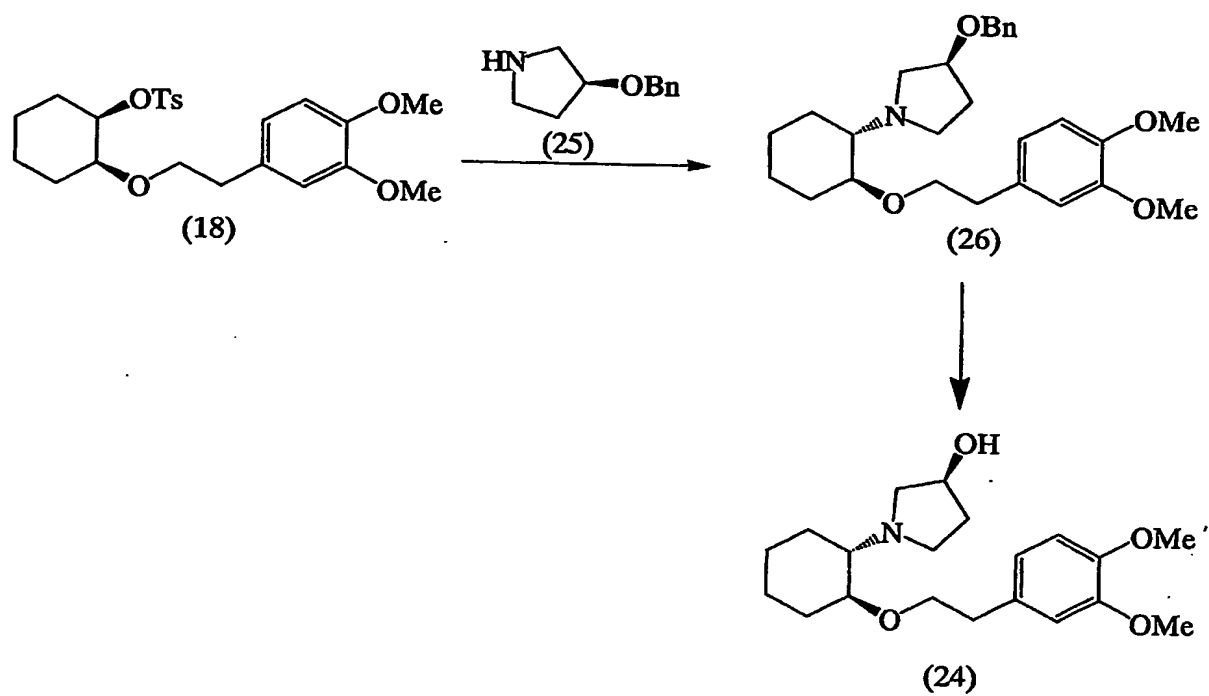
Scheme 20A

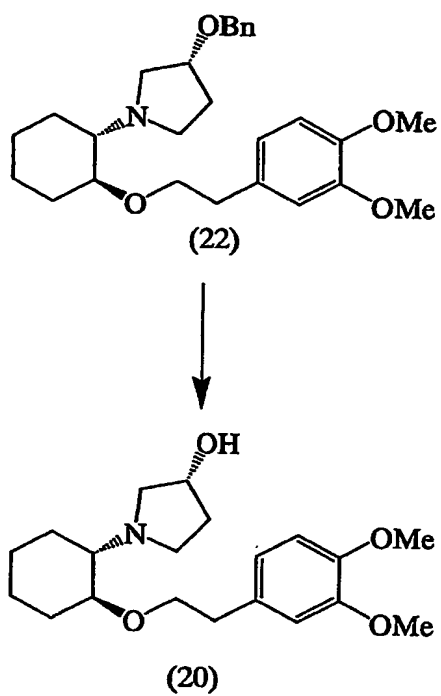


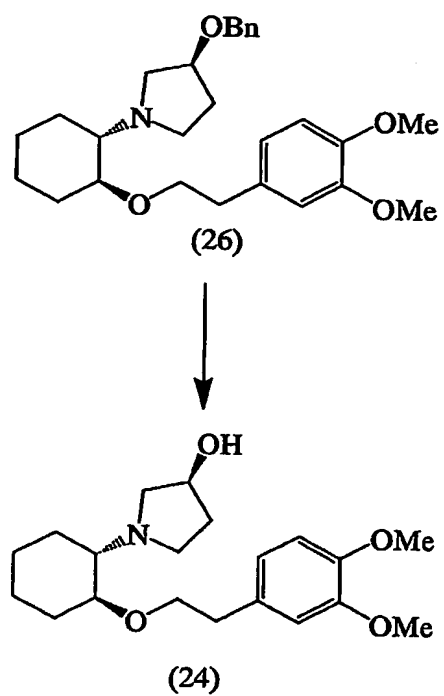


Scheme 20B

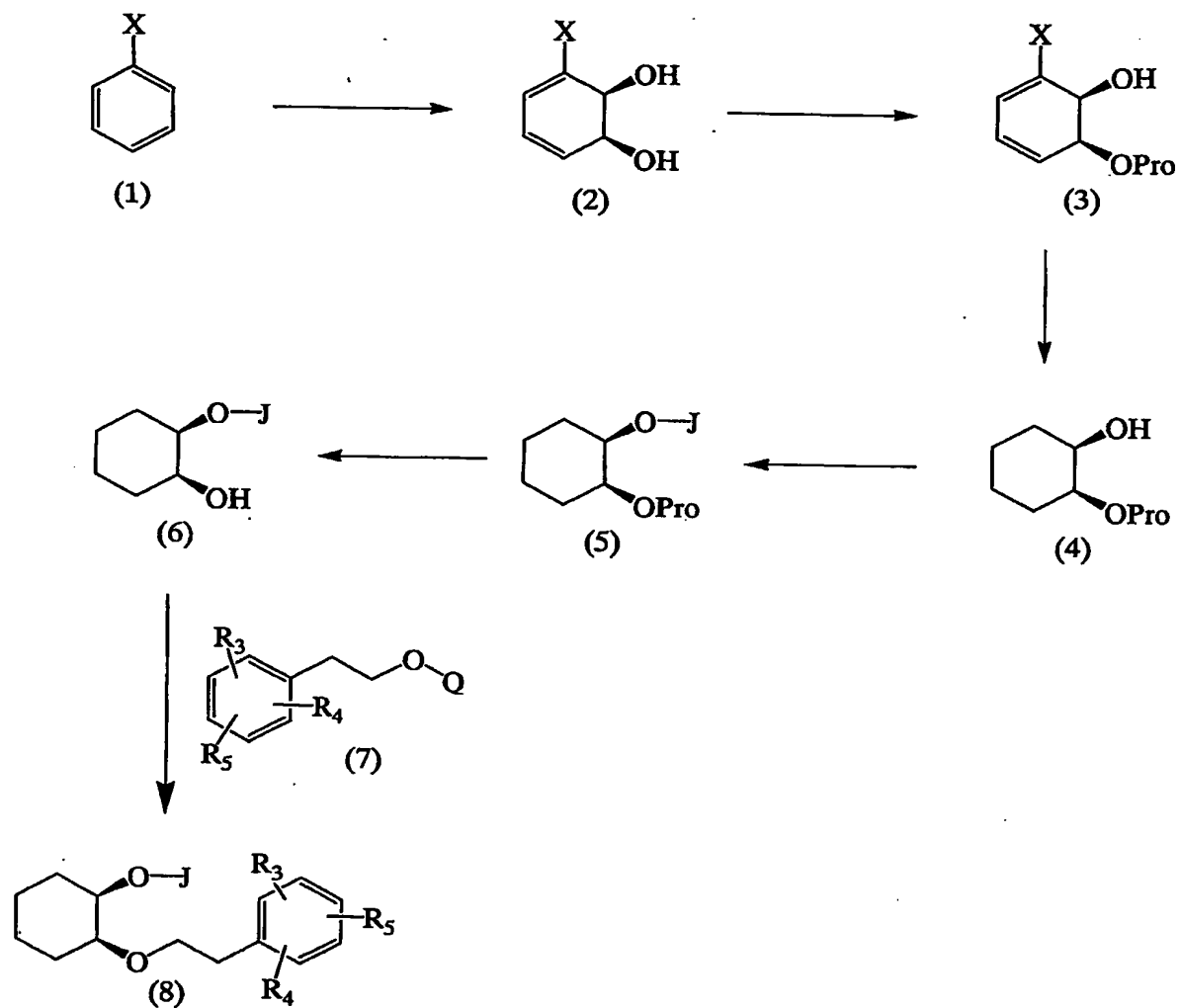
Scheme 21A

**Scheme 21B**

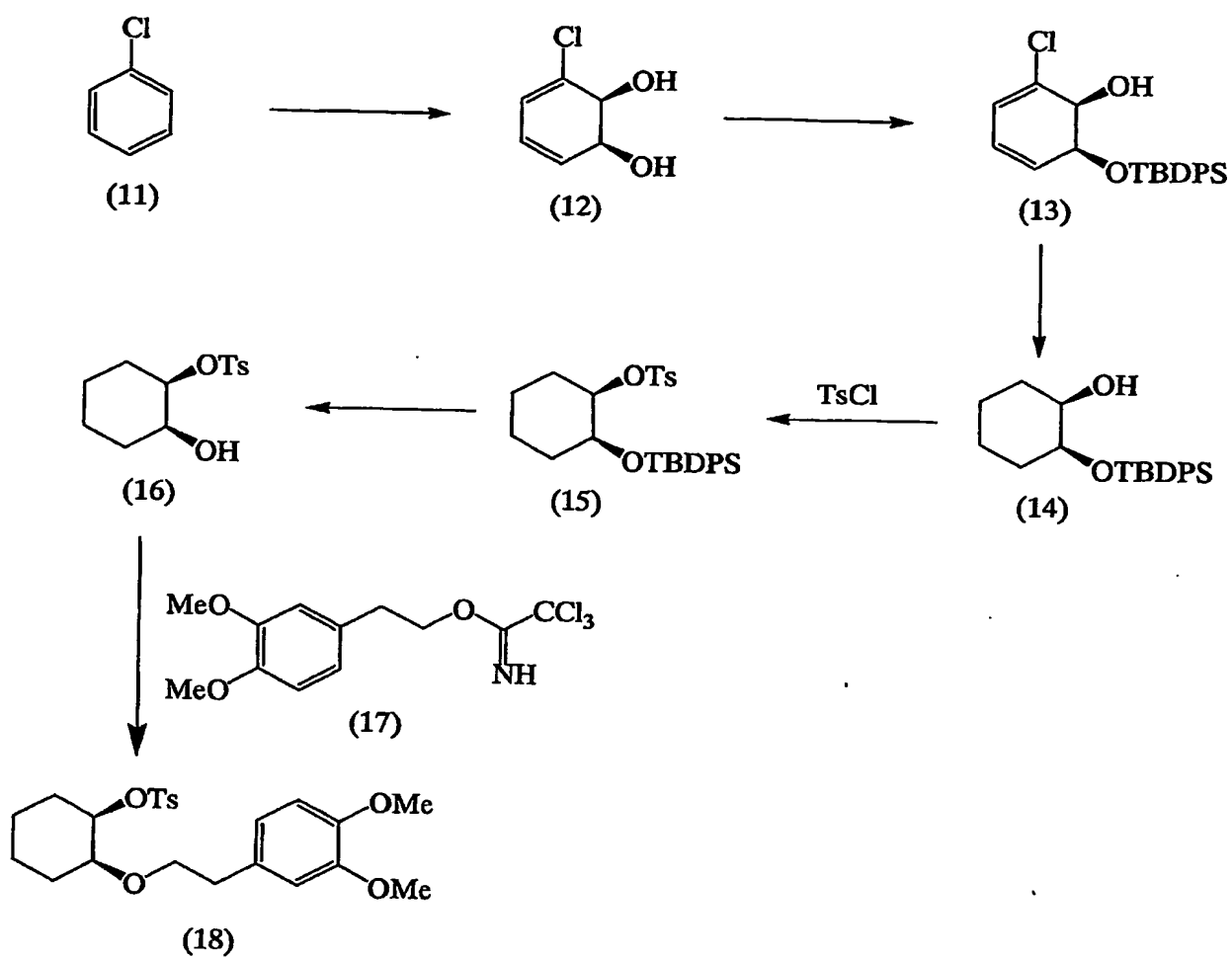
Scheme 22B

Scheme 23B

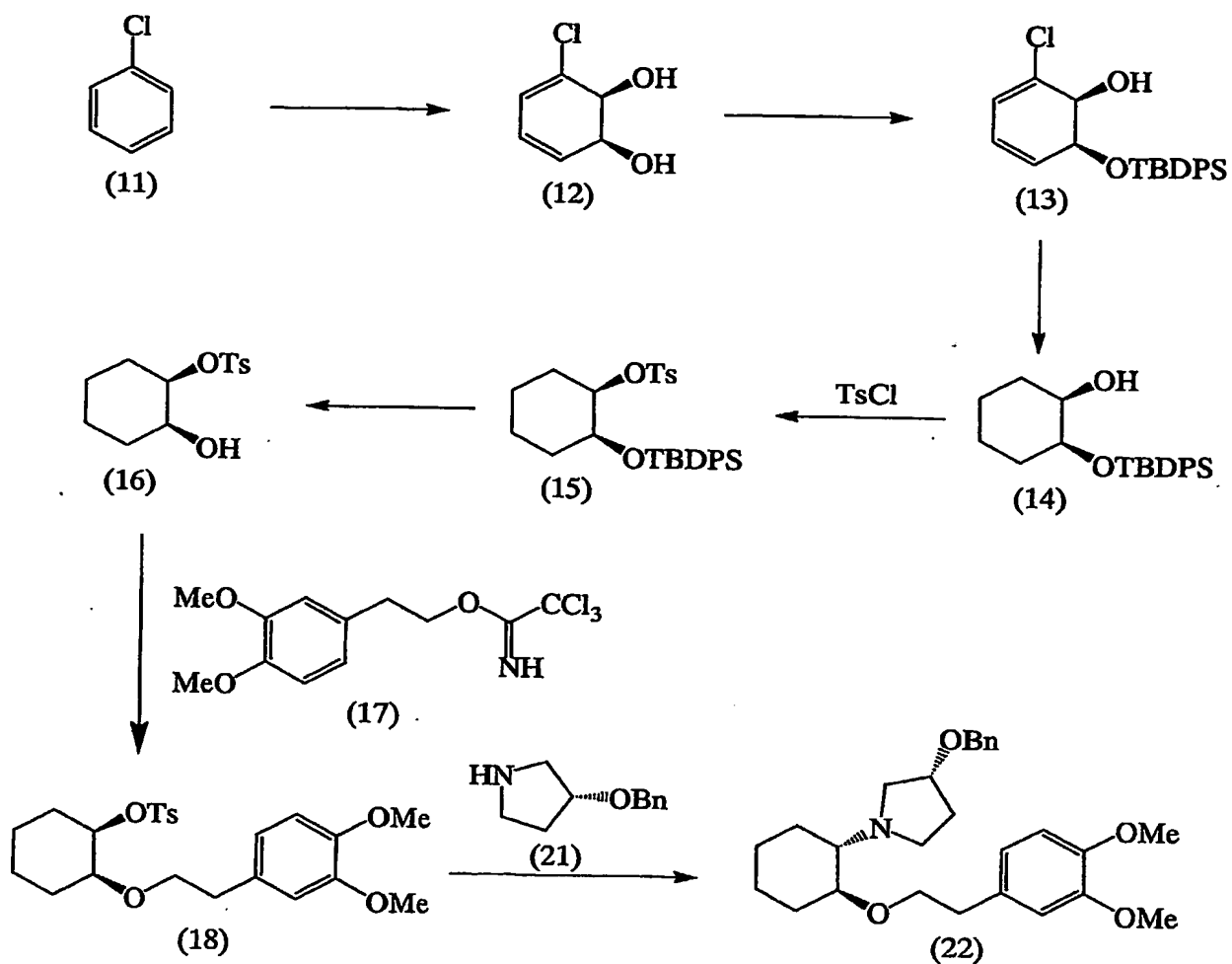
Scheme 24



Scheme 25A

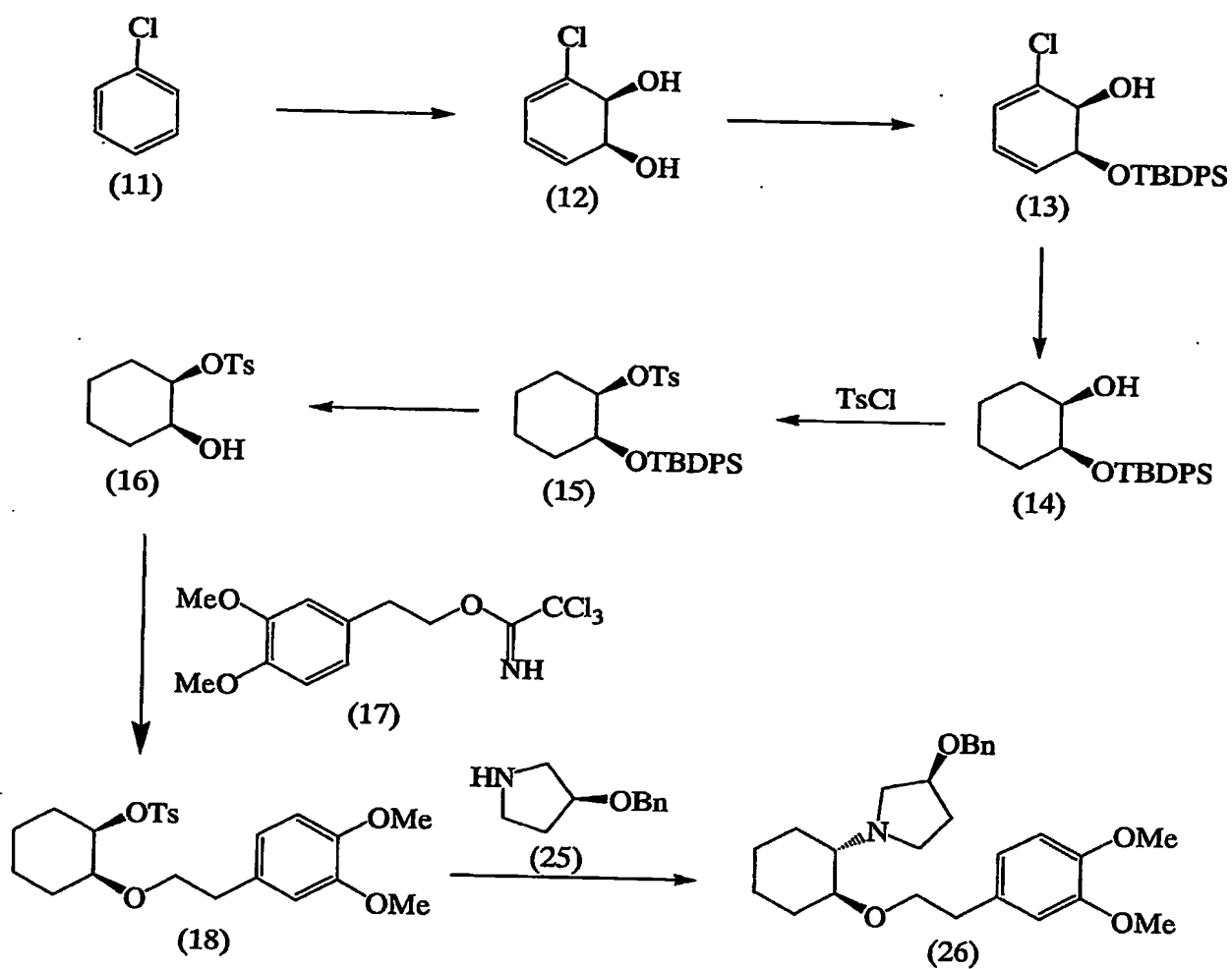


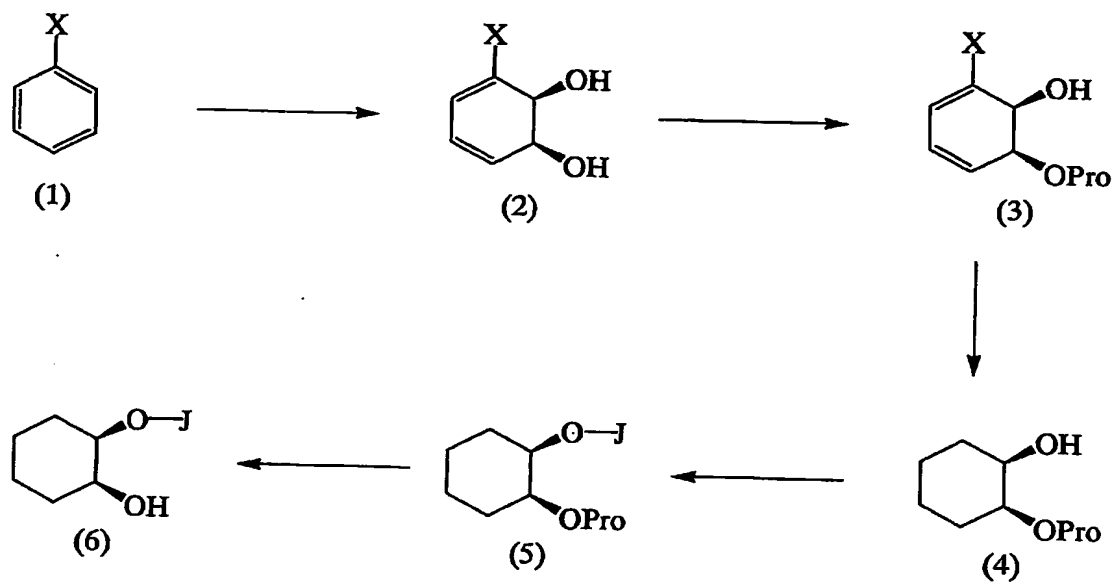
Scheme 25B

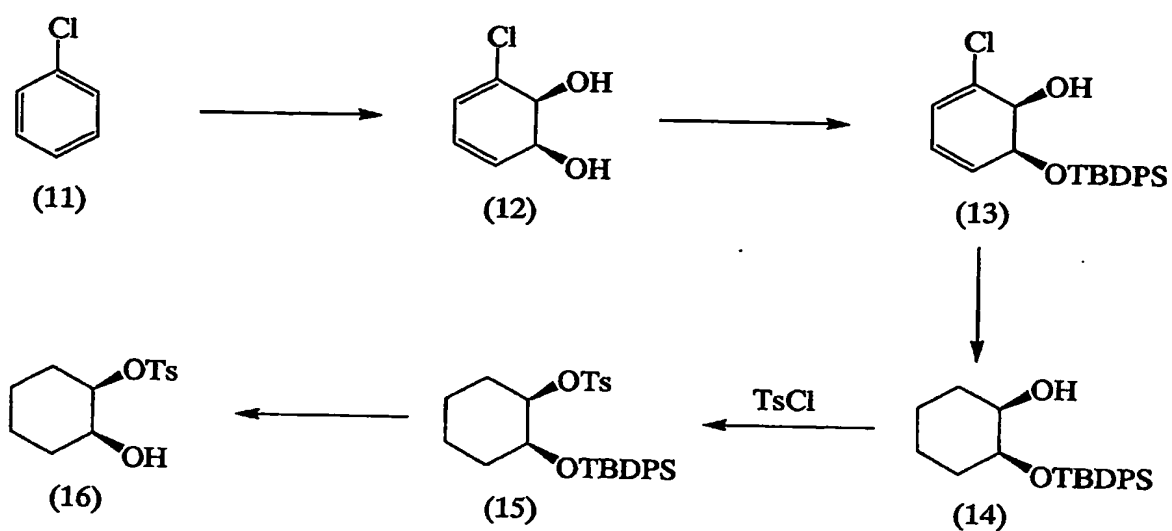


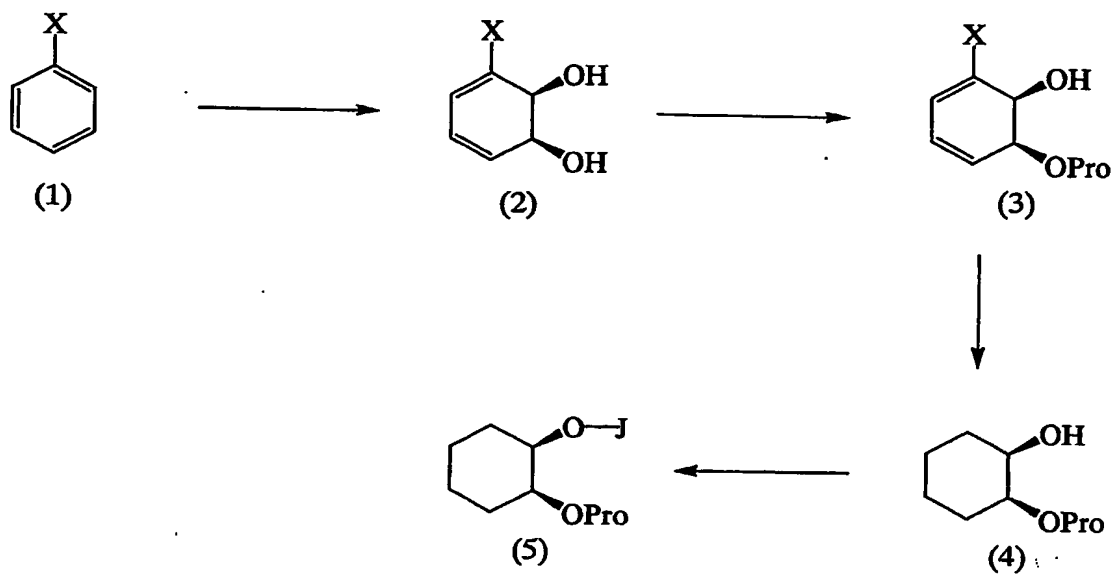


Scheme 26B

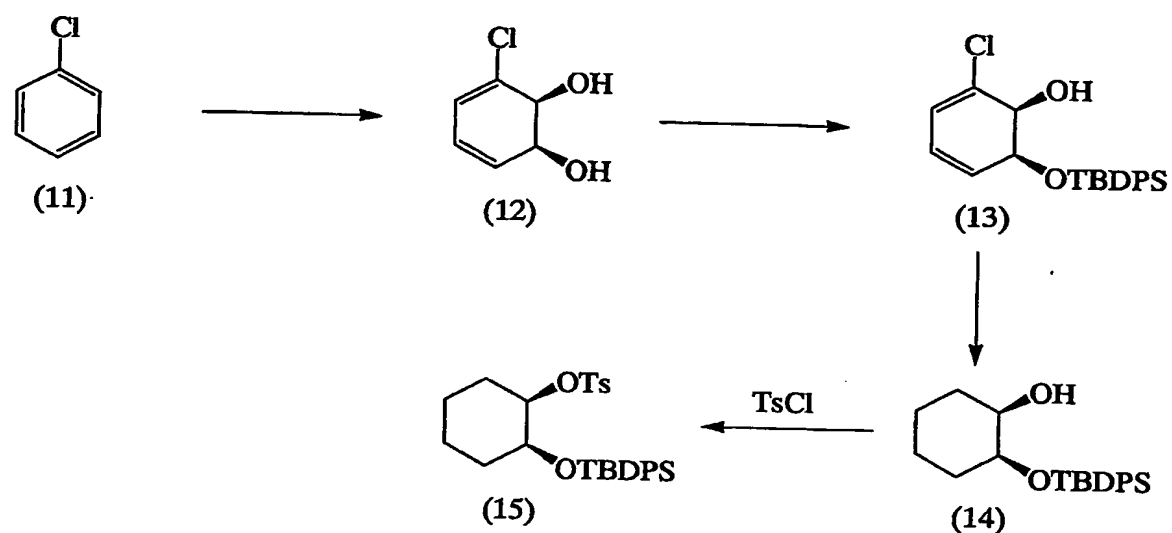


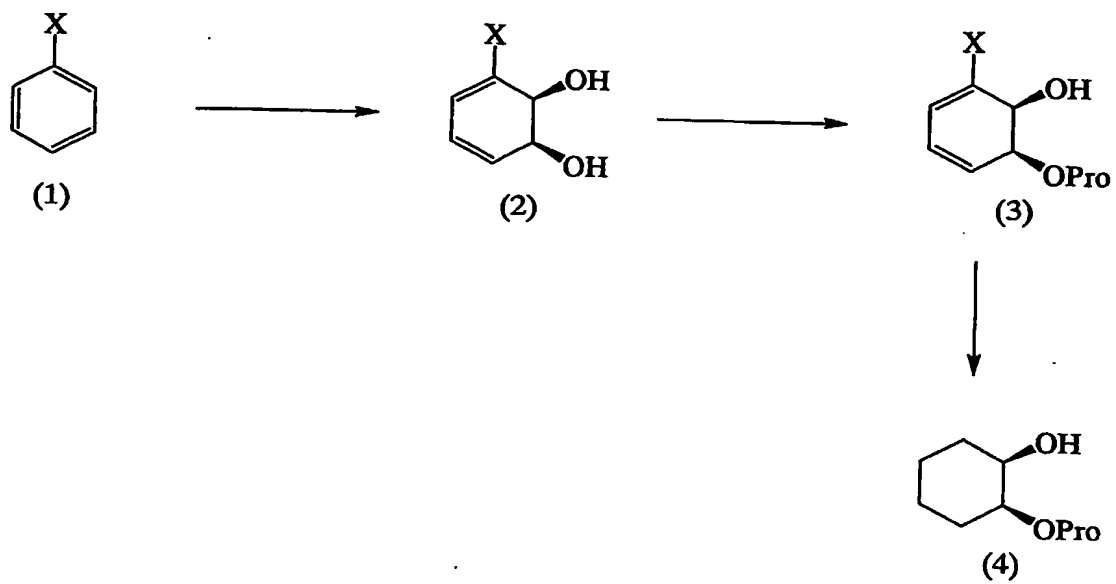
Scheme 27

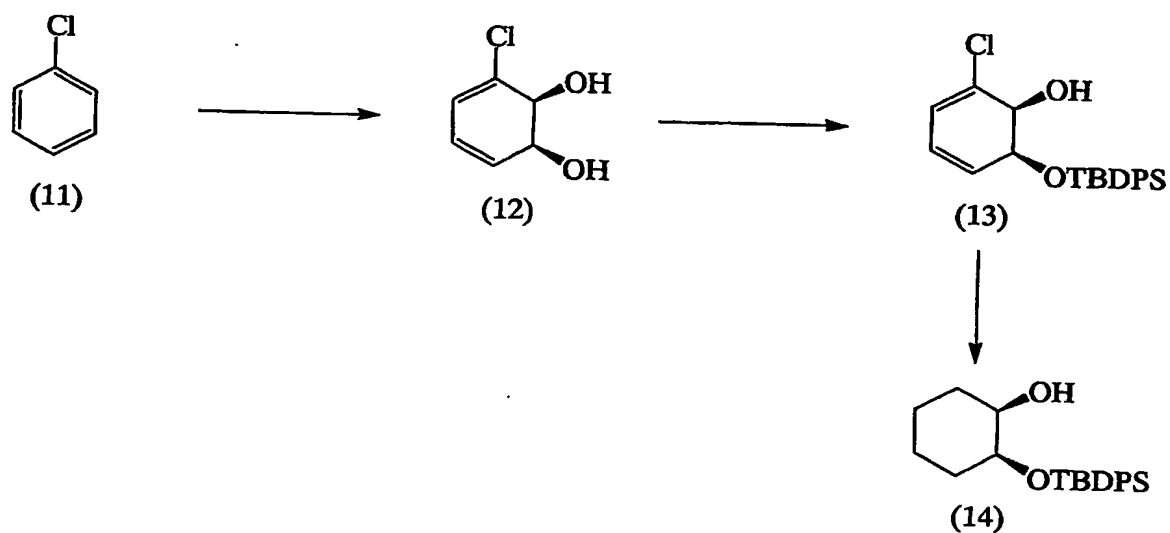
Scheme 28A

Scheme 29

Scheme 30A



Scheme 31

Scheme 32A

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